THE ROLE OF REAL-TIME ULTRASOUND IN THE ASSESSMENT AND MANAGEMENT OF PRETERM LABOUR

by

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No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning

TO MY FAMILY

ABSTRACT

In this thesis the use of real-time ultrasound in the assessment and management of preterm labour has been studied, with particular reference to the observation of fetal breathing movements, gross fetal body movements and the state of the uterine cervix. In addition, a longitudinal analysis of the trends in preterm labour in the John Radcliffe Hospital in Oxford between 1973 and 1981 has been performed. Finally, an attempt has been made to clarify the relationship between prostaglandin E2 and fetal breathing movements.

The analysis of the trends in preterm labour in Oxford has shown that the incidence of preterm delivery remains unaltered. Of these patients, however, those eligible for tocolytic therapy (unexplained spontaneous preterm labour) form a small proportion. The incidence of extreme prematurity in this group is very low and the neonatal outcome is good.

The presence or absence of Fetal Breathing Movements (FBM) by defined criteria is shown to be a highly sensitive index of whether the preterm labour is going to progress to delivery or not in singleton pregnancies with intact membranes. Its significance is lost when the membranes are ruptured and in multiple pregnancies. In pregnancies complicated by antepartum haemorrhage the presence or absence of Fetal Breathing Movements does not predict further haemorrhage leading to delivery. Fetal Breathing Movement status on admission bears no relationship to neonatal outcome and gives no indication of the presence of intrauterine infection. Silent chorioamnionitis has been highlighted as an important cause of "unexplained" preterm labour.

Gross Fetal Body Movements (FM) are shown to give no early indication of impending preterm delivery. Evidence is presented to suggest that significant diminution in Fetal Movements is related to poor neonatal outcome.

Ultrasonic measurement of the uterine cervix has been found to be technically feasible but of no benefit in the diagnosis of ongoing preterm labour.

The relationship between prostaglandin E2 (PGE2) and the cessation of fetal breathing movement has been approached by elucidating the maternal absorption of PGE2 from a vaginal pessary. This then enabled me to sample fetal blood at the time of maximal maternal concentrations (the time we expect the fetal concentration to be greatest). This was performed by fetoscopy and demonstrated that a significant rise in fetal bicyclo-prostaglandin-E-metabolite (bicyclo-PGEM) occurs following maternal vaginal administration of PGE2. Using this information FBM has been assessed two and a half hours following the vaginal administration of PGE2. No reduction in FBM was demonstrated. Although inconclusive, as the bicyclo-PGE metabolite is used to assess PGE levels, this evidence decreases the probability that PGE mediates the reduction in FBM with the onset of labour.

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CONTENTS

INTRODUCTION

Preterm delivery is a major cause of low birth weight and preterm infants represent a considerable part of modern perinatal care. Neonates born prematurely have an increased mortality and survivors are more likely to be handicapped than mature infants. World Health Organisation (WHO) statistics show that 21 million low birth weight (LBW) babies (weighing less than 2500g) were born throughout the world in 1979. These represented 17% of all births in that year and accounted for more than 75% of neonatal and infant deaths throughout the world. The differences between LBW and preterm infants (the latter defined by WHO as delivery before 259 days gestation) has recently been considered by Villar and Belizan (1982). In a large study of statistical rates from several countries, they concluded that the incidence of LBW could differ widely between developed and developing countries, but that that of preterm birth was rather similar in all these countries, at about 5-7%. Even after making adjustments for LBW, however, around 7,5 million neonates are annually delivered preterm throughout the world, a huge social, medical and economic problem.

With powerful tocolytic drugs available to clinicians for stopping labour it might reasonably be expected that when they are widely used the incidence of preterm delivery will be diminished. In practice this does not seem to be so. Both in Germany (Kubli 1977) and the United Kingdom (Turnbull and Anderson 1978), extensive use of tocolysis over a decade has caused no decrease in LBW. This disappointing discovery may be due, as Rush et al (1976) showed in Oxford, to the fact that 50% of preterm deliveries result from complications such as severe antepartum haemorrhage in which it is usually inadvisable to

arrest labour, or to severe pre-eclampsia, which can force the obstetrician to deliver the infant preterm to avoid more serious hazards such as intrauterine death. Rush et al also found that 12% of preterm labours occurred in the presence of a dead fetus or of gross abnormality incompatible with extra-uterine life.

Nevertheless, in about 40% of the preterm births they studied there were no maternal or fetal complications. It is in these cases that the greatest efforts have been made to arrest labour, particularly if the membranes were intact. Clinical trials of tocolytic drugs have given conflicting results about the efficacy of this treatment and there is controversy as to whether or not they should be used in clinical practice (King et al 1985). One of the greatest problems about assessing the efficacy of tocolytic drugs is the difficulty of making a certain diagnosis that preterm labour is established which will lead to delivery. In many women, apparently established in preterm labour, uterine contractions subside spontaneously. This diagnostic problem was illustrated by Anderson (1981) who reviewed the outcome of "preterm labour" in "control" patients, receiving only placebo treatment in randomised, controlled trials of uterine suppressant drugs. In approximately 55% of placebo treated patients, delivery had not occurred seven days after admission. Accordingly more than half the women admitted in preterm labour had needlessly been given powerful inhibitory drugs, with potential side effects for either mother or fetus.

The potential dangers of treatment should not to be underestimated. The most widely used tocolytics in clinical practice are the ₱Adrenergic agonist group. Carlsson et al (1972) have shown that there is no specific distribution of ₱1 and ₱2

receptors, but rather that the ratio of β1 to β2 receptors in different organs is different. This means that specific influence on a particular organ by one type of β-receptor agonist is probably not possible. Thus all current and future β-mimetic agents will affect the cardiovascular and other systems besides the uterus.

These side effects on the cardiovascular system have long been known. Following the initial publication by Bishop and Woutersz (1961) about isoxsuprine therapy there have been more investigations than can readily be reviewed here. However, probably the most serious and widely reported side effects of β-mimetic therapy is symptomatic or asymptomatic myocardial ischaemia (Katz et al 1981, Robertson et al 1981, Ying and Tejani 1982, Benedetti 1983). No particular drug was incriminated. The effect may be dose related and is of unknown incidence. Echocardiographic studies by Irmer (1980) have shown an increased strain on the heart throughout the entire period of therapy during pregnancy. In addition, Irmer found increased pulmonary capillary pressure with exercise in some patients 5 weeks after delivery, possibly indicating some disturbance of left ventricular function as a result of continuous β-mimetic therapy. It is not known if this disturbance of myocardial function is reversible or permanent. Recently Wolff et al (1982) measured lung capillary "wedge" pressure in patients receiving tocolytic therapy, and found no evidence of myocardial damage. In patients with silent pre-existing heart disease, however, the disorder could be aggravated by the administration of β-mimetics. Where a patient has a tendency to supine hypotension, even small doses of β-mimetic may considerably limit venous return. The β2 induced

peripheral vasodilation potentiates reduction in venous return and can, occasionally lead to a shock reaction in the mother (Grospietsh and Kuhn 1984).

Pulmonary oedema with β-mimetic therapy administered with or without glucocorticoids has been frequently reported (Elliot et al 1978, Abramovici et al 1980, Grospretsch and Kuhn 1984) and may occur in as many as 5% of cases (Katz et al 1981).

Renal function may be impaired (Grospietsch et al 1981) and the effects on uteroplacental perfusion remain unresolved. In pregnant ewes, a significant reduction in uterine blood flow has been demonstrated with a number of tocolytic agents (Ehrenkranz et al 1976, 1977a, 1977b, Siimes and Creasy 1979). There have been similar findings in the pregnant rhesus monkey (Myers et al al 1978) not supported by Martensson et al (1979) using ritodrine in pregnant guinea pigs, possibly reflecting a species difference. No human data is available.

Electrolyte and metabolic disturbances occur with intravenous β-mimetics. Hypokalaemia is the predominant electrolyte change and occurs with all known β-mimetics (Gross and Sokol 1980, Kirkpatrick et al 1980, Cotton et al 1981). Occasionally pathologically low serum potassium levels have been reported. Hypoglycaemia as a result of glycogenolysis with resultant hyperinsulinaemia may occur. β1-sympathomimetic-stimulated lipolysis induces increased plasma concentrations of free fatty acids, glycerin, triglycerides and ketone bodies. Glycogenolysis and lipolysis leads to a metabolic acidosis, causing hyperventilation and a fall in pCO2.

Adverse fetal and neonatal effects of tocolysis have recently been publicised. Brazy and Pupkin (1979) found an

increase in hypoglycaemia, hypocalcaemia, ileus, hypotension and death in infants exposed in utero to isoxsuprine compared with controls. Cardiac toxicity has been implicated with β-mimetic therapy (Vogt et al 1979) and has recently been reported in 5% of infants exposed to Fenoterol (Loser et al 1981). Kristofferson and Hansen (1979) followed 131 infants whose mothers had been treated with ritodrine and compared them with controls in a randomized double blind controlled trial. The ritodrine treated group required more resuscitation, experienced more respiratory distress and generally had worse neonatal outcomes. Long term cardiac complications have been documented by Freysz et al (1977), in infants born to mothers treated with ritodrine compared with matched controls. These included electrocardiogram changes and, in one case, left ventricular hypertrophy.

Adverse effects have been ascribed to other agents in clinical use. Zervoudakis et al (1980) found that maternal alcohol (ethanol) administration was associated with a significant increase in the respiratory distress syndrome (RDS) in the treated group (48%) compared with controls (13%). There were more neonatal deaths (19%) in the alcohol treated group than controls (13%) but this difference may not be statistically significant. These findings confirmed the earlier findings of Barrada et al (1977). Milner and Chouksey (1972) reported alopecia in all infants delivered following chronic maternal oral administration of the calcium antagonist, Diazoxide. Severe neonatal hyperglycaemia has been documented following intravenous Diazoxide administration (Neuman et al 1979, Milsap et al 1980) and animal studies have shown that it is capable of destroying fetal pancreatic islet cells (Boulos et al 1971). Prostaglandin

synthetase inhibitors (PGSI) can cause in-utero closure of the ductus arteriosus (Coceani et al 1976) and oligohydramnios (Manaugh and Novy 1976), leading to death in utero in fetal animals.

In man, PGSI's have been incriminated as causing persistent pulmonary hypertension of the newborn (Levin et al 1978, Goudie and Dossetor 1979, Wilkinson et al 1979, Rubaltelli et al 1979); coagulation disorders (Wilkinson 1980); and oligohydramnios (Itskovitz et al 1980) associated with perinatal death in neonates after failure of maternal tocolytic therapy.

The implications of this data are that the problems associated with preterm birth may well be compounded by the effects of attempted pharmocolgical prevention. Against this must be weighed the potential advantages if treatment is successful.

As I have noted earlier, reviews of clinical trials of tocolysis at the time work for this thesis began, indicated a marked "placebo" effect (Anderson 1977, 1981, Anderson and Turnbull 1982). Approximately 55% of the placebo treated women had not delivered within 7 days. Hemminki and Starfield (1978), in their review of 18 controlled trials looking for neonatal benefit, concluded that in only 2 of the trials could this be demonstrated. All these authors drew attention to the problem of establishing the diagnosis of true preterm labour ie: labour which, without inhibition, would progress to delivery of the infant.

In this context, the potentially harmful even lethal side effects of tocolytic drugs seem unacceptable hazards, when tocolytic treatment of patients in whom preterm "labour" will

spontaneously subside, is in fact unnecessary. A reliable means of predicting those women in early preterm labour who will deliver and those who will not, would greatly reduce such risks for many patients. It would also enable us reliably to assess the efficacy of current treatment regimes.

Attempts to discriminate patients in true preterm labour from those in whom pregnancy will continue have not previously been successful. Various clinical "scoring" systems have been described. In reviewing these, Liu and Blackwell (1978) concluded that clinical assessment of uterine contractions and the state of the cervix, the basis of many prognostic scoring systems, correlated poorly with outcome. Once the cervix was over 4cm. dilated, however, delivery was inevitable, but most women are less far dilated on admission. The most reliable predictive factor, ruptured membranes, generally precludes long-term tocolytic therapy because of a strong association with intra uterine infection. Prognostic criteria used in trials subsequent to Liu and Blackwell (Spellacy et al 1979, Creasy et al 1980, Merkatz et al 1980) have all used these unreliable parameters.

Risk prediction has also been unsuccessful. In reviewing attempts to formalize perinatal risk prediction mathematically Newcombe et al (1977) concluded that risk prediction rules performed spuriously well because they had been chosen deliberately to optimize performance in particular studies. When applied to a different database, they lost predictive efficiency. Using the Fedrick rule (1976) they were able to identify 18% of multiparous women at risk, in whom 82% of spontaneous preterm births would occur. However, 38% of primiparae had to be included to identify only 62% of the

spontaneous preterm deliveries. Information about previous preterm delivery was of greatest significance; all other risk determinants were relatively unimportant. The risk of preterm delivery in subsequent pregnancies has been studied by Bakketeig et al (1981). A woman whose first pregnancy went to term had only a 4,4% risk of preterm birth with her second infant, whereas if the first was preterm, the second was also preterm in 17,2% of cases. If two previous deliveries were preterm then the risk of a third one being so was 28,4%. Since first births had the highest preterm delivery rates, however, neither the Fedrick rules nor the study of previous obstetric history identify a major part of the problem.

The unreliability of current diagnostic criteria, the potential hazards of unnecessary tocolytic treatment to both mother and fetus, and our need reliably to assess treatment regimes prompted the research programme described in this thesis, designed to detect "true" and "false" preterm labour.

If we are accurately to diagnose early preterm labour and thus effectively identify those patients who may benefit from treatment with uterine suppressants, other parameters need to be developed. Ultrasound, which provides a window into the intrauterine environment, may provide us with these parameters. We are now able to observe and measure fetal biophysical parameters in utero and accurately measure the size of the fetus, placenta and uterus. It might be expected that a change from quiescent and continuing pregnancy to active labour could alter both the fetal behaviour pattern and the anatomy of the internal cervical os. In assessing the usefulness of ultrasound in the assessment and management of preterm labour I have concentrated

on the ultrasonic measurement of two biophysical parameters: Fetal Breathing Movements (FBM) and Total Fetal Body Movements (FM) and one anatomical parameter, the state of the cervix, for predicting labour outcome.

The association between fetal abnormality and preterm labour (Rush et al 1976) and the use of ultrasound in the diagnosis of these fetal anomalies (Hobbins et al 1979) is well established. Ultrasonic estimation of fetal size and weight, its accuracy and its effect on management, is established practice in some centres (Campbell 1977). I have not included these aspects in the research protocol although they form an integral part of the ultrasound assessment I have made of the fetus in mothers admitted in preterm labour.

Biophysical parameters have not previously been used for the prediction of labour outcome. The following section reviews the relationship between FBM and labour, its measurement by ultrasound and the factors which influence its occurrence. I have also reviewed the ultrasonic assessment of FM, the factors affecting its occurrence; and the ultrasonic assessment of the state of the cervix.

FETAL BREATHING MOVEMENTS

The concept that the fetus made breathing movements in utero in man is nearly a century old. In 1888 Ahlfeld, a German gynaecologist, published the first of his many publications on fetal breathing recorded with a kymograph. In 1899 an Italian contemporary, Ferroni, confirmed Ahlfeld's observations. These reports were reviewed in 1911 by the physiologist Reifferschied who published, for the first time, kymograph tracings showing similtaneously intrauterine fetal breathing movements, maternal respiratory movements and carotid pulse, all of which occurred at different rates. The older literature is of more than historical interest as, from the viewpoint of the 1980's, the recordings mentioned above are persuasive evidence of intrauterine fetal breathing and the interpretations of these early investigators are exraordinarily perceptive. Many of the observations made regarding the rate, episodic nature, frequency and duration of FBM and the existence of hiccups hold good today. Contemporary collegues, however, were not so impressed and the observations were declared false. Snyder (1937), in his translational review, quotes critics as saying "It is to be urged that this doctrine finally vanishes until data are actually brought forth on the living human or animal fetus which demonstrates "ad oculos" these intrauterine respiratory movements which, up to now are a completely vague assumption". This situation remained unresolved until 1970. Review of the pre 1970 literature (Wilds 1978) reveals that the majority of published work affirmed the prevailing belief of the time that FBM normally did not occur in utero.

Acute studies of fetal breathing in animals antedate any

observations of human fetal breathing by over a century. In 1781 Winslow observed breathing in fetal dogs and cats after the uterus had been exposed and before the umbilical cords were disturbed (Wilds 1978). Beclard, in 1813, described similar respiratory movements after opening the uteri of pregnant animals (Wilds 1978). He noted that disturbance of the placental circulation led to stronger and faster movements. The demonstration "ad oculos" required by Ahlfeld and Reifferschied's critics, demonstrating that observed movements of the maternal abdomen were the direct result of fetal breathing movements were a long time in coming. In experimental animals, investigators either failed to demonstrate the movements at all or were able to elicit them only under unphysiological conditions. Between 1936 and 1946 Barcroft and Barron dominated the work on fetal breathing in the U.K. and effectively laid FBM to rest for 25 years (Dawes 1984). Following acute experiments on sheep Barcroft concluded that, in fetal lambs, respiratory movements were normally inhibited after the 60th day and could only be elicited by asphyxia (Barcroft 1946). It was only when Dawes and Merlet similtaneously produced their work in 1970 that re-evaluation of the situation occurred (Dawes et al 1970, Merlet et al 1970).

Professor Dawes' personal account of the events leading to the "rediscovery" of fetal breathing and what subsequently transpired is of more than passing interest as it introduces many of the eminent investigators in this field. Between 1966 to 1968 Prof.Dawes was in California conducting research and writing his book "Fetal and Neonatal Physiology". In it he prophetically wrote that newborn animals were "evidently well prepared to

sustain continuous breathing activity after delivery and do not readily fatigue. It is hard to believe that they are wholly inactive in utero". While there he met and became friendly with Dr, now Professor G.C.Liggins who was working at Davis University near San Francisco on amniotic fluid and its relation to fetal lung function. In discussions, they questioned Barcroft's work and in 1969, on a visit to New Zealand, Prof. Dawes arranged for Liggins to spend a sabbatical year in Oxford, in 1970.

Prior to his arrival, in the autumn of 1969, Prof Dawes received, by accident, a group of 20 sheep of the same gestation and decided to use these to repeat Barcroft's original experiments. He found that Barcroft's conclusions had been incorrect for he was able to demonstrate breathing when the fetal lambs were delivered into warm saline baths. This re-examination was prompted by work done with Claudia Merlet and others (Dawes et al 1969), in which brief episodes of breathing movements had been induced by injection of cyanide into both carotid arteries. This gave rise to the possibility that breathing was inhibited by experimental conditions. Thus, by the time Liggins arrived in January 1970, the winds of change had begun to be felt in the "Tower of the Winds" of the Nuffield Institute for medical research, the old Radcliffe Observatory which housed the experimental laboratory now part of Green College (Personal communication Prof. Dawes).

Using the method introduced by Barron and his collegues in Yale for making observations on the unanaesthetised fetal lamb in utero, by chronic implantation of catheters (Barron et al 1965) Dawes and Liggins inserted a tracheal catheter into their first experimental lamb (Personal comm.G.S.Dawes). On leaving a

pressure recording device on line overnight, they found episodic recordings of fetal breathing movement. This they confirmed by delivery of the fetus into a warm saline bath. They also noticed that this episodic FBM occurred during rapid eye movement (REM) sleep, which is also episodic. By this time Ruckebusch had developed the technique for implanting eletrodes in the fetal skull for recording the fetal electrocorticogram (ECOG) (Ruckebusch 1971). Using this technique Dawes et al (1972) implanted ECOG electrodes and tracheal catheters and confirmed the association between REM sleep (low voltage ECOG) and FBM. They also demonstrated that fetal pO2 did not change before the onset, or cessation of FBM (Dawes et al 1972). This remarkable series of discoveries, which have been confirmed by all investigators who have studied this phenomenon, were made over a three month period when Liggins was in Oxford and set in motion intensive investigation into FBM, which continues today.

During their experiments, Dawes and Liggins noted a dramatic reduction in FBM in two fetal lambs which became hypoxic. Robinson and Boddy had joined the Nuffield Institute in 1971 and the phenomenon of reduced FBM with fetal hypoxia prompted them to consider whether FBM occurred in the human fetus as postulated in 1888 and whether a similar reduction in FBM was associated with intra uterine fetal asphyxia. To investigate this, a non-invasive technique was required. By this time ultrasound had been developed by Prof.Ian Donald in Glasgow. This was the A-Scan, an ultrasound with a one dimensional display on an oscillascope screen. Using the A-Scan, Boddy and Robinson recorded fetal chest wall movements by first identifying the fetal heart echo and then locating the fetal chest wall. Chest

wall movements were recorded using an electronic "gate" (Boddy and Robinson 1971). The method was validated by measuring chest wall movements in fetal lambs, in whom the thoracic pressure changes were also being recorded similtaneously by means of a catheter implanted some days previously (Boddy and Dawes 1975).

Following this initial report, FBM was observed by many others using A-Scan (Wilds 1978). However, the limitations and difficulties of the technique together with its inherent errors later highlighted by Farman et al (1975), necessitated better imaging techniques. In 1974 Harold Fox and John Patrick were working with Prof Dawes in Oxford and both concluded that the real-time ultrasound imaging which had just been developed by ADR* in the U.S.A. could resolve many of the problems with the identification and recording of FBM. They returned to Rochester, New York and London, Ontario Canada respectively resolved to utilise the ADR equipment for this purpose. The scene was now set for objective ultrasonic assessment of intrauterine fetal activity.

* Advanced Diagnostic Research Corporation, Tempe, Arizona, U.S.A. .

Ultrasound Recording of Fetal Breathing

Recordings of FBM using ultrasound may be achieved by four methods:-

1. A-Scan : pulsed ultrasound with one dimentional display.
2. M-Mode : multiple time-position display.
3. Doppler Ultrasound
4. Real-time B-Scan : pulsed ultrasound with a two dimentional display.

A-Scan

As already mentioned, the first ultrasonic measurements of human fetal breathing movements were made by Boddy and Robinson using an A-Scan. This is pulsed ultrasound with a one dimensional display on an oscillascope enabling the technician to select the echoes from the fetal chest wall having initially observed the heart beating. Following their initial report, with a method validated in chronically catherised fetal lambs, many reports by Gennser, Marsal, Boddy, Mantell and Manning (Wilds 1978) were published. The relative movements of echoes from opposite sides of the fetal chest wall have been measured. This has been made possible by the development of a tracking system by Mantell in Auckland (Mantell 1976) and Marsal in Malmo (Marsal et al 1976). Mantell reported that the anterior chest wall had an excursion of 4-7mm per breath but that posterior echoes near the spine were relatively fixed. He was the first to observe the paradoxical movement of fetal chest and abdomen with fetal breathing.

Although A-Scan has been effectively used by experienced investigators to confirm many observations made in chronically catheterised fetal animals, the limitations of the technique

preclude its widespread use in clinical practice and have raised serious doubts about the quantitation of human FBM in clinical studies. Errors and artefacts of several types have been described by Farman et al (1975). Errors can arise from artefactual movements of the ultrasound transducer on the maternal abdomen, or movement of the fetus resulting from maternal aortic pulsations, uterine contractions, maternal respiration, coughing, maternal muscular activity, placental pulsation, gross fetal body movements or fetal heart activity. Boddy (1976a) estimated that 20-25% of A-Scan recordings were uninterpretable because of such errors. The ultrasound beam has to be at right angles to the fetal chest wall to obtain optimal recordings. This may be achieved by passing the beam through the mitral valve, or by prior orientation with a B-Scan. Whenever the fetus moves, however, the angle of insonation changes, altering the recordings. It is therefore impossible for the observer to know whether the disappearance of fetal chest wall movements is due to fetal apnoea, or to a change in fetal position.

The other error with A-Scan results from the swept-gain control setting required to compensate for echo attenuation at deeper tissue levels. This may lead either to a failure to identify FBM of small amplitude, or to erroneous interpretation of small artefactual movements as FBM. Farman et al amply demonstrated this by producing recordings identical to FBM, from non-pregnant uteri and other organs, by deliberate misuse of A-scan. In spite of these artefacts and errors Marsal (1977) has reported a high degree of inter-and-intra-observer agreement in the interpretation of records. Although the improvements in

gating and swept-gain control systems described by Farman et al (1975) and Meire et al (1975), and the tracking devices of Mantell and Marsal, have provided the possibility of more accurate interpretation of the A-Scan, it is not a clinically viable technique.

M-Mode

The use of multiple time-position displays of an A-Scan device have been used to identify the artefacts that have plagued A-Scan. Tremewan et al (1976) measured movement of both chest walls similtaneously. Bots et al (1976) used M-Mode display of a linear array scanning system to make recordings of fetal chest wall movements. Like the A-scan, however, this method is also influenced by the alignment of the transducer relative to the fetus, giving rise to errors similar to those with A-Scan.

Doppler ultrasound

During FBM, high velocity doppler shift signals are generated within the fetal chest and upper abdomen. Continuous - wave doppler systems utilising these signals to generate audible signals and measure velocities, have been used for many years to record fetal heart activity. Bishop (1966) described rhythmic sounds from the pregnant uterus that were not synchronous with either the fetal heart, maternal pulse or respiration. Boyce et al (1976a) recognised these as representing fetal breathing activity. Using a Sonicaid D205 instrument, these investigators made audible recordings of doppler sounds during human FBM, detected by means of strain gauges on the maternal abdomen (Boyce et al 1976b). Gough and Poore (1977) confirmed that these sounds were of venous origin and Goodman and Mantell (1980) described hearing two distinct sounds during typical fetal breathing.

Using a range-gated doppler instrument which was focussed through a real-time scanner, these investigators demonstrated that the "Oxford" sound reported by Boyce et al originated in the area of the fetal inferior vena cava, and was always cephalad with respect to the fetus. This system has the advantage of permitting detection of very small breaths. However, the signals may be influenced by the effects of the cardiac cycle on venous flow (Wilds 1978). Continuous-wave doppler systems deliver higher doses of ultrasound to the fetus than pulsed systems and in the light of recent concerns with ultrasound exposure and its safety this may be important. Thaler et al (1980) claim that continuous wave Doppler is at least as reliable and accurate for the detection of FBM as real-time scanning. Doppler recorded data by Thaler et al (1980) and Goodman (1980) suggest that the occurrence of FBM is similar to that recorded with real-time systems but no prolonged measurement studies are available nor has the average incidence of FBM been calculated for investigations with this method.

Real-time ultrasound

Hohler and Fox (1976) demonstrated that real-time B-scan had sufficient resolution to measure fetal breathing movements. They enumerated the advantages of real-time over the other methods of ultrasound as

"1. Orientation is rapidly ascertained and maintained throughout the examination.

2. Timing of specific chest wall movements is sharply defined.

3. Other motions are quickly recognised and discounted.

4. The possibility of quantitation of fetal chest wall

movements now exists."

In 1977 the same investigators published validatory experiments on chronically instrumented fetal rhesus monkeys (Fox and Hohler 1977). Measuring fetal tracheal pressure and similtaneously observing FBM with a real-time scanner on the surface of the maternal abdomen, they observed movements of the fetal chest and abdominal wall with the smallest changes in tracheal pressure. Manning (1977b), confirmed these observations also using fetal monkey preparations.

The methods of quantitation of FBM are visual interpretation from the display screen and automated systems. Bots et al (1976), Wladimiroff et al (1976) and DeWolf (1976) describe automatic systems combining B-and A-mode scans with M-Mode recording systems. Here, an M-Mode display of echo signals from one of the units in a linear-array transducer is recorded for analysis. Similar automated measuring systems which record the distance between echoes and produce analogue outputs have been used by Lindstrom et al (1977) and Marsal et al (1978c). Cousin (1980) has pointed out the limitations of these systems in accurately measuring small changes, caused by variations in the amplitude of echoes and has developed a phase-locked, amplitude independent tracking system combined with a real-time scanner. This very accurate system has a resolution to the nearest 2u. It is extremely complex and expensive, however, and most research about FBM has resulted from visual interpretation of real-time scanners and/or video recordings.

The chief shortcoming of real-time visual data is the need for a human observer to interpret the display and the inherent inaccuracies of recording breath-to-breath intervals by pressing

a button. The method allows the observer to estimate the incidence of breathing activity and permits approximate estimates of all but the fastest breathing rates. Because of the inconsistencies of human reaction times, however, it is inadequate for recording breath-to-breath intervals. Wilds (1980) considered this an important shortcoming because variability was an important criterion of normality. Trudinger et al (1979) measured breath-to-breath intervals in growth retarded fetuses and found them to be reduced. This aspect of FBM has not been explored further.

Patrick et al (1978a) have studied variation among trained observers in the detection of FBM. One hour videotape recordings were independently analysed by different observers. The correlation coefficient among observers was 0,94 and the average difference among observers was 2,5%. Visual interpretation therefore seems accurate for determining the incidence of FBM. Its value was not assessed for measuring the amplitude or frequency of FBM.

There are two ways of observing human FBM with a real-time scanner. Firstly, longitudinal scanning of the fetal trunk can be performed as described first by Campbell et al (1977), then by Patrick et al (1978b) and later by Ritchie (1979). This permits visualization of the fetal chest and abdominal wall. During each fetal breath the anterior chest wall moves inward 2-5mm and the anterior fetal abdominal wall moves outward in the opposite direction, 3-8mm. When posterior chest wall echoes are not directly over or near the fetal spine, both chest walls can be seen to move inward, towards each other, 2-5mm. Following each inspiratory movement, the fetal chest and abdominal walls return

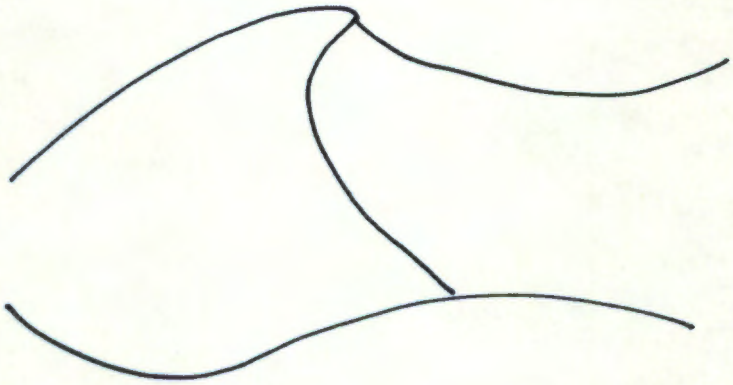
to their resting state. These paradoxical movements of fetal chest and abdominal wall echoes (fig 1) permit identification of each FBM (Patrick et al 1978). In this description the authors stated that the amount of chest and abdominal wall movement varied and that echoes from the fetal diaphragm and liver could be seen moving downward into the abdomen during inspiration. With the improved resolution of current ultrasound systems, this is a striking feature and the diaphragm is frequently clearly visualised.

The second method employed is a transverse view of the upper fetal abdomen as used by Roberts et al (1979, 1980a). This method was used since Patrick et al (1978b) had shown that gross fetal movements were sufficient to prevent the recognition of FBM. FBM are recognised by rythmical movements of the fetal abdominal wall perimeter outward and inward, and downward movement of the abdominal contents. Using this transverse method Roberts et al had no difficulty in visualizing FBM during and after large excursions of the fetal body. They may not be visible with a longitudinal view. The mean incidence of concurrent trunk and breathing movements is small , about 2% according to Roberts et al (1980a). Values obtained by Patrick and Roberts using the two methods are sufficiently similar to suggest they are of similar accuracy.

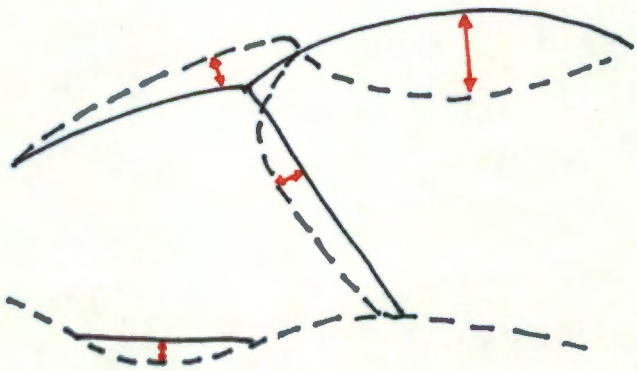
In my own study, a real-time ultrasound scanner was used to obtain a longitudinal view of the fetal chest and abdomen. As has been demonstrated, this method is accurate and unencumbered by the artefacts of the other ultrasound methods.

fig 1

REAL-TIME ULTRASOUND OBSERVATION OF FETAL BREATHING MOVEMENTS



RESTING STATE



INSPIRATION/EXPIRATION

Fetal Hiccups

At this stage, it is necessary to draw attention to the phenomenon of fetal hiccups. These movements are qualitatively similar to breathing movements but of low frequency, high amplitude and usually of short duration. The movements are violent and often noticed by the mother. They have been described by Lewis and Trudinger (1977), Lemay et al (1977) and Patrick et al (1978b). Ultrasonic studies show that the hiccups can occur either during periods of fetal breathing or during fetal apnoea; they are apparently a normal phenomenon. Bots et al (1978) found an increased incidence in growth retarded fetuses (not a statistically significant increase), and advocated further studies. Wittman et al (1983) reported an increased incidence of fetal hiccups with intra uterine fetal growth retardation, congenital anomalies and in fetuses of diabetic mothers. No conclusive proof has been presented of any pathological significance. Since most normal fetuses exhibit this phenomenon at some time it may well have no significance. There is no relationship between fetal hiccups and FBM and it is important, when recording the latter, to distinguish it from hiccups. This is not difficult since the fetal hiccup is a short, violent movement with little rhythmicity.

Normal Characteristics of FBM

The Rate of FBM in normal pregnancies during the third trimester is 50-60 breaths/minute (Campbell et al 1977, Marsal 1978a, Patrick et al 1980b). Studies by both Patrick et al (1980b) and Trudinger and Knight (1980) document a change in the pattern of FBM with advancing gestation. Both groups noted that the breathing rate slows and becomes more regular. Trudinger

describes changes in breathing "configuration" with advancing gestation. This is "short and panting" up to 32-34 weeks, followed by multiple inspiratory movements with a prolonged inspiratory phase and a short expiratory recoil, between 32 and 36 weeks. Thereafter FBM is of a more uniform character. Both groups speculate that these changes are due to the development of lung reflexes and central nervous system control.

Periodicity

From the first observations by Ahlfeld (1888) it has been noted that FBM are irregular and episodic in nature both in animals and humans. This episodic behavior of FBM activity presents difficulties when attempts are made either to measure the phenomenon experimentally or to utilise its presence in applied clinical situations. To define fetal apnoea in utero Patrick et al (1980a), using computerised measurements, found that of successive breath-to-breath intervals in fetuses between 30 and 39 weeks gestation, only 3% were separated by 6 or more seconds. Thus fetal apnoea could be defined as a period in which successive FBM were separated by 6 or more seconds. Of great clinical significance has been the documentation by the same group of the duration of normal apnoea. In their classic paper Patrick et al (1980a) demonstrated that the longest period of apnoea in normal pregnancy at 30-31 weeks was 65 minutes, at 34-35 weeks 105 minutes and at 38-39 weeks over 120 minutes (recent, unpublished data puts this last period quoted at 180 mins - Patrick; personal communication).

Because of its episodic nature, the duration of a recording can substantially influence the incidence of FBM. Using mathematical auto-regression, Campbell et al (1980b) analysed 24

hour records of FBM recorded in Patrick's study. She concluded that the occurence of FBM was non-random and that the minimum observation time to estimate overall FBM incidence would be 100 minutes.

The mean Incidence of FBM found in studies using real-time scanners varies. Ritchie (1979) found FBM 27,6% of the time, Patrick et al (1980b) 31% and Roberts et al (1980a) 37%. The only 24 hour records are those of Patrick and Roberts who have demonstrated clearly that the incidence of FBM remains unaltered between 31 and 40 weeks gestation. An earlier study by Fox et al (1979) indicated that FBM increased with increasing gestational age. This data, however, comprises short periods of recording and the 24 hour studies are more convincing. Prior to 31 weeks Roberts et al (1980a) and Trudinger and Knight (1980) have documented a decreased incidence of FBM.

In the first reports on FBM in humans considerable diurnal variarion in incidence was found (Boddy and Dawes 1975). This finding was confirmed by real-time scanning by Patrick et al (1978a) and Roberts et al (1979). During their 24 hour recordings a marked circadian rhythm was noted. Both investigators demonstrated a minimum of FBM around 2400 hrs. Patrick showed the lowest incidence to be between 2200 and 0100 hrs, whereas Roberts demonstrated the minimum between 0100 and 0400 hrs. Patrick shows a significant increase in FBM 2-3 hours following maternal meals and between 0400 and 0700 hrs. while the mothers were asleep. The postprandial incidence in Roberts' study increased but did not reach statistical significance. However, the patterns of FBM demonstrated by these investigators showed a circadian rhythm, with increased FBM relating to

maternal meals. This will be discussed later.

Patrick et al (1981a) postulated that maternal glucocorticoids might influence FBM, and the increase seen between 0100 and 0700 occured at the same time as the rise in maternal peripheral plasma cortisol. In a study of women treated with synthetic glucocorticoids, no overnight increase in FBM occurred, suggesting that endogenous glucocorticoids might play a role in the circadian rhythm of human FBM (Patrick 1982a).

Factors influencing FBM

These are many and varied. The development of chronic fetal animal preparations, particularly the fetal lamb by Dawes et al (1970) and the fetal Rhesus monkey by Martin et al (1974), has been a major step in understanding the physiology of FBM. Species differences may exist but these are the only models in which direct information about the physiology and regulation of FBM may be obtained. Most initial observations were made in animals and the phenomenon found and subsequently sought in the human by indirect methods (mainly ultrasound).

Fetal Behavioural States

Dawes et al (1972) reported the now well known association between FBM and rapid eye movement sleep in fetal lambs. These investigators demonstrated a pattern of rapid, irregular breathing movements, varying in rate and amplitude, accounting for over 90% of FBM and consistently associated with low voltage electrocortical (ECOG) activity and REM sleep. A second pattern of large slow movements (1-4/min) occurred and bore no relation to the ECOG activity. In the human fetus, rest-activity cycles may be indirectly assessed by ultrasound and fetal heart rate pattern changes, without confirmatory ECOG. Carse et al (1980)

described FBM as resembling the breathing activity seen in the newborn during active sleep. They also pointed out that it might also occur during quiet sleep and concluded that "it is possible that in human fetuses, unlike the lamb, breathing may not be completely inhibited during quiet sleep, perhaps because the high voltage state is not fully developed in the human at term".

Junge and Walter (1981) analysed the behavioural states of the human fetus with eight hour recordings of FBM, fetal movements and fetal heart rate. They distinguished active and quiet sleep states, documented a complete cycle of active+quiet sleep as lasting 75 mins. and noted that quiet sleep accounted for less than 30% of the cycle. This concurs with the mathematical analysis of FBM patterns by Campbell (1980a) who found that 90% of all motor activity in the fetus occurred during active sleep, strikingly similar to what happens in fetal lambs. Nijhuis et al (1981) confirmed the existence of differing human fetal behavioural states and found them similar to those in low-risk preterm infants. They observed fetuses with two real-time scanners, recorded general movements, FBM, fetal eye and mouth movements and fetal heart rate. Recently, attempts have been made to arouse fetuses when asleep, to stimulate FBM, fetal heart rate and fetal movement (Richardson et al 1981a, Visser et al 1981). Physical stimulation, however, does not change the incidence of FBM.

Maternal Glucose Concentration

The first published observations that FBM may be affected by maternal plasma glucose concentration were made in sheep by Boddy and Dawes (1973, 1974a). They noted that the incidence of FBM was greatly reduced when fetal plasma glucose fell to 10mg/100ml

(0,5mmol/l) and that FBM was abolished when the fetal plasma glucose levels fell below 8mg/100ml (0,4mmol/l). The normal fetal plasma glucose concentration in the lamb is 15-25mg/dl (0,75-1,4mmol/l) (Shelley et al 1975). Fetal hypoglycaemia was induced by failure of the ewes to eat after surgery. Martin et al (1975) induced fetal hypoglycaemia in rhesus monkeys by maternal and fetal administration of insulin. They also produced fetal hyperglycaemia by maternal intravenous infusion of 20% glucose solution. They found no consistent relationship between rapid changes in fetal plasma glucose concentrations and the incidence of FBM.

Natale (1980) demonstrated that continuous intravenous infusion of glucose to the fetal lamb, producing hyperglycaemia of up to 50mg/dl (2,8mmol), was associated with an increase in FBM. However, the delay between the infusion begining and the onset of increased FBM was variable and up to two hours in length. The increase remained episodic and only during periods of REM sleep. Richardson et al (1981b) have recently demonstrated that infusions of glucose into pregnant ewes results in an increase in FBM but that this does not occur in ewes which had been fed prior to the experiment.

Following the initial reports by Dawes and Boddy on the apparent relationship of FBM to plasma glucose concentrations in the sheep, these workers published work in humans using A-scan (Boddy, Dawes and Robinson 1974), demonstrating increased human FBM following maternal intravenous glucose administration. Shortly thereafter Fox et al (1976), using a real-time scanner, reported an increase in FBM 20 minutes following oral administration of a 75gm glucose load in 8 of 9 patients studied.

This was confirmed by Lewis et al (1978). In their 24 hour studies between 30 and 39 weeks gestation Patrick et al (1980b) documented that human fetuses made breathing movements for a greater percentage of the time during the second and third hours following a standard 800 calorie maternal meal. Maternal plasma glucose concentrations seemed to increase prior to the increase in FBM, suggesting some modulating mechanism. Roberts et al (1978) described a significant correlation between the maternal plasma glucose level without loading and FBM incidence.

The effect of glucose loading both orally and intravenously has been documented by a number of investigators. Controlled studies comparing changes in FBM incidence following oral glucose, saline or water administration and intravenous glucose confirm the earlier uncontrolled work (Natale et al 1978, Gelman et al 1980, Goodman 1980, Bocking et al 1982). Natale (1980), in a well controlled set of experiments, documented the time lag between glucose administration (oral and intravenous), peak in maternal plasma glucose concentration and the peak in FBM incidence. Following oral loading the maternal level peaked at 60 minutes and FBM at 105 minutes (45min after the maternal plasma glucose). The intravenous time scale is very similar, with FBM peaking 45min. after a bolus injection of 25gm of glucose.

The natural hyperglycaemic state of the pregnant diabetic patient has provided further information. Patrick et al (1978b) documented large variations in the incidence of FBM in the same fetuses of diabetic mothers depending on the maternal plasma glucose. FBM were present 80% of the time when the maternal glucose levels were greater than 180mg/dl (9mmol/l), and less

than 5% at 40-50mg/dl (2-2,5mmol/l). Roberts et al (1980b) and Roodenburg and Wladimiroff (1981) have shown that the increase in FBM incidence following maternal meals is more prolonged than in normal pregnancies.

All the above studies were performed on fasting patients subsequently fed. Studies on non-fasting mothers by Fox and Hohler (1977) and Lewis and Boylan (1979) showed no difference in FBM incidence before and after oral glucose loading, although the initial FBM incidence was greater than in the fetuses of fasting mothers. Patrick (1982) describes a study where mothers were fed a 600 cal. meal containing only fat and protein and pre- and postprandial FBM and maternal glucose levels were measured. No significant increase in either maternal plasma glucose concentration or FBM incidence was found postprandially.

Thus, from the reported work on the influence of glucose on FBM, it appears that maternal fasting and hypoglycaemia inhibit FBM, while a rapid increase in maternal, and thus fetal, blood glucose, stimulates FBM. Although the incidence of FBM is affected, rate and pattern are not. In the nonfasting state, however, this direct correlation is not apparent - a situation similar to that found in experimental animals. The explanation for this phenomenon is unclear. Natale et al (1978) postulate a metabolic mechanism. In sheep (Boddy et al 1974a) and human fetuses (Ritchie and Lakani 1978) maternal and fetal hypercapnia is associated with increased FBM. The central chemoreceptors are sensitive to local increases in carbon dioxide (CO2) governed by local metabolism, cerebrospinal fluid and blood flow. The brain utilizes glucose as its energy source and by aerobic oxidation produces water and carbon dioxide. Natale postulates local

increase in glucose metabolism, with increased local tissue CO2 content, as the cause of FBM stimulation.

There is, however, another possible mechanism. From neonatal observations, hypoglycaemia may be responsible for apnoeic attacks (Davies et al 1972). In addition, glucose is known to stimulate REM sleep in the neonate (Harper et al 1977) suggesting that the phenomenon may be caused by the direct action of glucose in altering electrocortical activity.

Cigarette Smoking

Initial studies, utilising A-scan, by Manning et al (1975), Manning and Feyerabend (1976) and Gennser et al (1975), suggested a decrease in FBM incidence following cigarette smoking. It was also demonstrated that nicotine chewing gum reproduced the effects and that smoking non-nicotine (herbal) cigarettes produced no effect. Manning and associates (1977a) injected nicotine into the aorta of pregnant ewes. This decreased FBM, which was accompanied by, and attributed to, hypoxaemia.

These investigators concluded that the decrease in FBM following maternal smoking was related to fetal hypoxaemia due to direct or indirect effect of nicotine on the uterine and/or placental blood flow. The A-scan, however, is very inaccurate (see earlier) and more recent studies have failed to confirm earlier findings. Thaler et al (1980), using continuous doppler ultrasound, previously validated (Gough et al 1977, Goodman and Mantell 1978) could find no change in FBM incidence with smoking but showed that the rate of FBM was increased. Recently, Sindberg-Eriksen et al (1983) reported decreased breath-to-breath intervals and increased FBM rate with smoking. They confirmed the findings of Thaler et al that the incidence of FBM

remained unchanged. This last study used real-time ultrasound.

Alcohol

Fox et al (1978) were the first to report the effect of ethanol on human FBM. Within 31 minutes of maternal ingestion of loz. of 40% alcohol, FBM were supressed in 7 patients between 37 and 39 weeks gestation. No changes in blood glucose were seen and the maternal blood alcohol level was very low. As the maternal alcohol level decreased with metabolism , FBM increased. Patrick (1982) quotes preliminary data by McLeod et al (unpublished) supporting Fox's findings and suggests that very low quantities of alcohol (0,25gm/kg) administered near term may result in FBM suppression for 3 hours or more.

Breaching of the Membranes

There are conflicting reports in the literature on FBM response to altering the state of the membranes. Manning et al (1977a) noted a significant decrease in FBM for up to 48 hours after amniocentesis in 24 high-risk pregnancies. Two further studies have failed to confirm this and report FBM incidence to remain unchanged after amniocentesis (Gennser and Marsal 1979, Hill Platt and Manning 1979). At fetoscopy in the third trimester we have noted no change in FBM either during or after the procedure (Castle and Mackenzie, unpublished observations).

Artificial rupture of the membranes prior to the onset of labour has been found to stimulate FBM (Wladimiroff et al 1979), have no significant effect on FBM (Richardson et al 1979) and to inhibit FBM (Boylan and Lewis 1980).

Blood gas tensions

In their definitive paper, Dawes et al (1972) documented that in one fetal lamb, significant hypoxia substantially reduced

FBM. Following this, Boddy et al (1974a) demonstrated a 100% increase in FBM activity when the fetus was rendered hypercapnic by exposing the ewe to a 4-6% CO2 gas mixture which also maintained fetal pO2 within normal limits. Hypoxaemia, however, led to an immediate arest of FBM, whereas hyperoxia had no perceptable effect.

Similar experiments have been performed in man. In normal pregnancies the findings were as in the experimental animals above. Ritchie and Lakhani (1980a) exposed pregnant women to a mixture of 5% CO2 and air for 15mins. and measured a threefold increase in FBM. Earlier, Wladimiroff et al (1978) had administered a 10% CO2-air mixture for 5 minutes and reported that FBM increased in most fetuses but not in those exhibiting intrauterine growth retardation. Ritchie and Lakhani (1980b) administered a 50% oxygen-air mixture and found no change in FBM incidence in normal fetuses. In pregnancies complicated by severe pre-eclampsia or fetal growth retardation, however, a significant increase in FBM was observed.

Drug administration

In the experimental animal model (mainly the sheep) numerous drug effects have been studied. Boddy et al (1976b) studied the effects of small doses of pentobarbital (4mg/kg) given intravenously in late pregnancy, and demonstrated a marked reduction in FBM following administration. Similar findings were reported by Condorelli and Scarpelli (1976) using various barbiturates. Pethidine, however, caused no consistent change in the incidence of FBM (Boddy et al 1976b). Recently, Rigatto et al (1984) reported that morphine infusion in the ewe initially inhibited, and then stimulated, FBM (after 10-15min). Piercy et

al (1977), using an intravenous infusion of 0,18-0,22mg/kg of diazepam, documented a reduction in FBM after infusion with FBM returning to normal within one hour. Piercy et al (1977) also studied the effects of caffeine and doxapram given directly to the fetus and reported that both stimulated FBM. Caffeine stimulation was transient, lasting only 3-5mins. Hogg et al (1977) also reported that doxapram stimulated FBM when infused into the ewe. Brown et al (1981) found that Pilocarpine in small doses stimulated FBM and considered this to be mediated by increased peripheral and/or central chemoreceptor sensitization.

Catecholamines such as adrenalin, noradrenaline and isoproterenol stimulate FBM when given by slow infusion to fetal lambs (Boddy et al 1975). Murata et al (1979) have reported similar findings with isoproterenol in chronic fetal rhesus monkey models. It is not clear if this is a direct effect, or mediated through increased plasma glucose concentration.

Kitterman et al (1979) demonstrated that infusions of Prostaglandin synthetase inhibitors (PGSI) into fetal lambs or pregnant ewes caused a dramatic increase in FBM incidence during the first 12 hours following infusion. Kitterman et al (1980), also report reduction in FBM with prostaglandin E2 infusion. Prostaglandin F2α infusion caused little reduction in FBM and no decrease in FBM followed endoperoxide infusion. More recently, Patrick et al (1981b) and Wallen et al (1984) have demonstrated increased FBM within 4 hours of PGSI infusion, but noted a return to normal within 12 hours, despite continuing PGSI infusion. Patrick et al (1981b) documented an increase in maternal and fetal plasma glucose concentrations during the first 16 hours of infusion, a finding which complicates interpretation.

In contrast to the animal data just documented, drug effect studies have only been conducted in human patients being treated incidentally with various drugs. Marsal et al (1975) investigated 29 pregnant women between 29 and 35 weeks gestation who were at risk of preterm delivery. Nineteen received Betamethazone daily and 10 who did not were used as controls. No effect on FBM incidence was found. There are conflicting reports on the effects of various narcotic and sedative drugs. Gennser et al (1976) reported that Meperidine (Pethidine) decreased FBM while Lewis and Olivier (1980), in a double blind study, demonstrated no effect. Boddy (1977) suggested that diazepam reduced FBM but Lewis and Olivier (1980) failed to confirm this. Barbiturates, caffeine and αMethyl-Dopa seem to have no consistent effects. Salbutamol has no effect on FBM (Lewis and Olivier 1980). Gennser et al (1976) reported one case in which Terbutaline infusion stimulated FBM. These studies on human pregnancy are on very small numbers and need verification.

Labour

In 1973 Dawes suggested that FBM was reduced in fetal lambs prior to the onset of labour, either term or preterm. Boddy and Dawes (1975) documented this reduction as significant and not associated with any change in blood gas values or plasma glucose concentration.

Studies of FBM in labour in man are preliminary. Using A-scan methods Boddy et al (1974b) documented reduction in FBM prior to and during normal labour at term. Wittman et al (1979), using real-time ultrasound, observed fetal activity in 25 patients in labour (mean gestational age 39 weeks). Nine of these labours were spontaneous and 16 were induced. The incidence of

FBM in labour was considerably reduced and when FBM occurred it did so in short (less than 30 second) bursts. It was demonstrated however, and absence of any fetal activity for 45 minutes or more correlated significantly with an abnormal fetal heart rate pattern. These investigators concluded that "reduced or absent fetal respiratory movements and decreased total fetal activity may indicate a fetus at risk".

Richardson et al (1979), studying FBM in electively induced labours at term in 20 patients, documented progressive reduction in FBM from pre-induction through latent to active labour, when the incidence of FBM was 0,8% of the observed time. All labour outcomes were normal. The authors concluded that the absence of FBM during electively induced labour at term did not indicate fetal compromise. Boylan and Lewis (1980) confirmed cessation of FBM in both induced and spontaneous labour at term as normal and, in addition, documented that maternal glucose infusion in labour did not stimulate FBM.

In the sheep, uterine contractions have been demonstrated to suppress FBM and alter fetal sleep state by Nathanielz et al (1980). Recently, Thaler et al (1984) have demonstrated a similar lack of FBM during contractions in the human.

Presentation

Marsal et al (1978b), using A-scan, suggested a reduction in FBM in the leading twin when the presentation was cephalic but not breech. They found a similar reduction in FBM in singleton pregnancies when the presentation was cephalic but not breech. This finding has not been confirmed when a real-time system was used (Angel et al 1978), suggesting possible inaccuracies in the A-scan system.

It is clear that FBM is influenced and affected by a large variety of factors and circumstances and is itself irregular and episodic in nature. It is a very sensitive index of fetal well-being and the fetus' interaction with its enviroment. It is this relationship between FBM and fetal enviroment that I have explored. With the onset of labour at term FBM is reduced with no ill-effect on the fetus. Since the major clinical dilemma in preterm labour is the difficulty in establishing, early on, which patients will naturally deliver preterm (over 50% do not), the possibility that reduced FBM in early labour might identify women actually at risk of delivering too early, has been the main concern of investigations described in this thesis.

FETAL MOVEMENTS

Maternal perception of fetal movements has been a sign of fetal life and well-being through the centuries (Genesis 25:22 Preyer 1885). Information about fetal movements has been derived from a number of techniques (Sorokin and Dierker 1982) but it was not until the introduction of B-mode ultrasound, with real-time observations of fetal activity, that reliable identification of fetal activity in utero could be catalogued. The first descriptions of ultrasonic observations of fetal movements (FM) were made by Hoffman et al (1967) and later by Reinold (1976). Since then extensive data about FM has accumulated from observation with real-time scanners.

The limitations and difficulties in recording FBM with various methods of ultrasound apply equally to FM. I will confine my review to real-time scanning observations.

FM was first studied using this method by Patrick (1977) and Roberts et al (1977). The shortcoming of this two-dimensional technique in the third trimester is that simultaneous observation of the entire fetus is not possible. In spite of this limitation, however, ultrasound is the most reliable technique for recording FM (Gettinger et al 1978, Hertogs et al 1979, Rayburn 1980, Sorokin et al 1981). The most widely used method for the quantitation of FM by real-time ultrasound, is a simple event marker system. The question of operator variability in assessing events was addressed by Roberts et al (1979). They investigated the reproducibility of FM records by repeated examination of videotape recordings of real-time images. Good inter-and-intra-observer reproducibility was found.

Before using this biophysical parameter clinically it is

necessary to establish normal fetal activity patterns and incidence and the factors that affect them.

Normal characteristics of FM

Many attempts to classify FM have been made. Birnholz et al (1978) describe 9 separate spontaneous movement patterns in normal pregnancies from 6 weeks to term. Several patterns correlated well with gestational age. Ianniruberto and Tajani (1981), studying 2000 pregnancies from 8 weeks to term, described 19 developmental milestones with increasing gestation. These two groups have provided important information on fetal motor neurodevelopment. Their observations are complex and not easilly interpretable. Patrick et al (1982b) described a more practical approach in 24 hour recordings of FM in the third trimester using real-time ultrasound. Three general types of FM were described; stretching, rolling and isolated extremity movements. So far no particular type of FM has emerged as significantly related to any specific abnormality. DeVries et al (1981) found, in a longitudinal study, that all movements seen in term fetuses were already present by 15 weeks gestation, but of different periodicity. Roberts et al (1980a) found that between 28 and 34 weeks gestation, movement episodes were shorter than in later gestation.

Fetal Rest-Activity Cycles (RAC) have been recognised for some time. Ruckebusch et al (1977) related sleep state (high and low voltage) and wakefulness to fetal activity in fetal lambs. Sleep states were recorded for 90% of the time over 24 hours while wakefulness occupied only 10%. Activity occurred during both periods but that accompanying fetal wakefulness was more frequent and intense at night. Sterman (1967), using strain

gauges and maternal perception, found human fetuses to have RAC in the third trimester. Timor-Tritsch et al (1978) identified activity periods in normal pregnancies at term using tocodynamometers. The mean duration of one complete cycle was 62 minutes. The average active period occupied 40 minutes and quiet period 22 minutes. In preterm fetuses between 28 and 30 weeks Sorokin and Dierker (1982) found significantly more RAC per hour than in term fetuses (6,6 compared with 2,2). They concluded that this cycling occurred less frequently and was of longer duration with increasing gestational age.

Junge (1979), in a farsighted observation, made recordings antenatally and subsequently postpartum on the same fetuses. He was able to show that movement patterns, heart rate patterns and behavioural states were probably a continuum and identified cycles of approximately one hour duration in the fetus that corresponded to non-REM and REM sleep cycles in the neonate. This work was confirmed and extended by Junge and Walter (1981). In 1981 Nijuis et al, using this principle, observed intrauterine fetal activity ultrasonically and found rest/activity behaviour similar to that in the preterm neonate (Prechtl et al 1979).

In their 24 hour continuous recordings Patrick et al (1982) demonstrated prolonged periods of fetal rest between 31 and 39 weeks. They found that these rest periods could extend for up to 75 minutes but that only 1% of intervals of 45 minutes or more contained no FM. This data is important when designing a study utilising this biophysical parameter. Campbell (1980) analysed Patricks dataset mathematically and found repetitive rhythms of FM in cycles of 60 to 150 minutes which were non-random.

The mean <u>incidence</u> of FM in normal pregnancy during the

third trimester range from 9 to 18% of time (Ritchie 1979, Roberts et al 1980a, Patrick et al 1980b). No change in FM incidence between 28 weeks and term was found by Roberts et al (1979) and this was later confirmed by Patrick et al (1982) in 24 hour records. A daily range of 5% to 15,3% was noted. The incidence of FM during these latter recordings was 10,2% of the time and, bearing in mind the observer continuity, are probably most accurate. The rate of FM was 30,8±1,2 movements/hour but, as might be expected, a very large range between 0 and 130 FM occurred. This wide range in the hourly and daily count of FM in any given woman has been noted by all observers (Sorokin and Dierker 1982).

A diurnal variation has been noted in normal pregnancies by Roberts et al (1979) and Patrick et al (1982). An increase in FM occurs between 2100hrs and 0100hrs, opposite to the pattern found with FBM, which are reduced over this period.

Factors effecting FM

Maternal serum glucose levels

The effects on FM of maternal glucose loading have been studied. As noted earlier this causes a significant increase in FBM after fasting. This, however, does not seem to be the case with FM although the data is conflicting. Patrick et al (1982) found that the incidence of FM between 31 and 39 weeks gestation was unrelated to maternal meals or plasma glucose concentration. Lewis et al (1978) and Natale et al (1978) studied the effect of a 50gm glucose load on FM measured ultrasonically and could demonstrate no increase.

Roodenburg and Wladimiroff (1981) studied FM in normal and diabetic pregnancies between 29 and 32 weeks gestation. They

could demonstrate no change in FM following breakfast and lunch but showed a significant increase after dinner. Diabetic pregnancies were associated with more FM than normal pregnancies. In a study using tocodynamometers and maternal perception Miller et al (1978) demonstrated significantly increased FM within 30 minutes of a 100gm glucose load for an oral glucose tolerance test. However, no correlation between the maternal plasma glucose concentration and FM could be found. Gelman et al (1980), using ultrasound, found increased FM following an intravenous glucose load in experimental patients as compared with controls. Aladjem et al (1979) studied the effect of an oral glucose load on FM and fetal heart rate (FHR). They concluded that lack of increase in FM was associated with increased perinatal morbidity and mortality. However, recording was by maternal perception and the investigators suggested that the increased FM perceived may have been FBM. Thus, although the data is conflicting, most investigators have not demonstrated an increase in FM associated with meals or glucose loading.

Pregnancy Pathology

Intra-uterine growth retardation (IUGR) is associated with a decrease in FM (Trudinger et al 1978, Roberts et al 1978) when compared with normal controls. Iannirubertо and Tejani (1981) documented a reduction in FM in pregnancies complicated by severe pre-eclampsia, rhesus isoimmunization and central nervous system anomalies. In animals hypoxia in utero has been shown to significantly reduce fetal lamb forelimb movement (Natale et al 1981, Sorokin and Dierker 1982)

External stimuli

Richardson et al (1981a) found that ultrasonically measured

FM were unchanged by physical stimulation of the fetus. Using shaking of the uterine fundus and balloting of the fetal head suprapubically they found no change in either FM or FHR variability compared with the control period prior to the stimulus. Visser et al (1981) also detected no significant change in FHR patterns or FM as a result of shaking the abdomen of 10 normal pregnant patients during episodes of low FHR variability. These findings conflict with those of Lee and Drukker (1979) and Keegan and Paul (1980). They recommended physical stimulation of fetal activity for inducing FHR accelerations during periods of non-reactivity in the non-stress test for fetal evaluation. No ultrasound was used by these two groups, however, so reliable FM identification could not be performed. Recently Rabinowitz et al (1983) have investigated the relationship between FHR accelerations and FM using real-time ultrasound and a doppler FHR monitor. They demonstrated that all FM seen on ultrasound were associated with large FHR accelerations (>15 beats/minute lasting 15 seconds or more). Thus the validity of the findings of Lee and Drukker, and Keegan and Paul cannot be ruled out. Aladjem et al (1977) noted that physical stimulation of fetal head and neck elicited an increase in FHR over the baseline of 13% lasting 27 seconds. Richardsons data was calculated as the mean over a 5 minute period and it is possible that an acute FHR and FM response to external stimuli may be too short-lived to reach statistical significance when 5 minute intervals are measured. Thus, the matter remains unresolved and FM may be stimulated by physical manipulation of the fetus. This is important as ultrasound assessment may follow abdominal palpation.

Exposure of the fetus to sound stimulus applied to the maternal abdomen caused an increased number of FM observed (Gelman et al 1982). Sound of higher frequency was required (2000 cycles per second of 110 decibels) to cause this, as 500 cps (110db) had no effect.

Amniocentesis has been shown to cause a significant increase in FM (Hill et al 1979).

Drug effects

The effects of cigarette smoking on FM have been carefully studied by Sindberg - Eriksen et al (1983). They reported no change in the incidence of FM following smoking but a change in FM pattern with clustering of FM the significance of which is unknown. Recently Goodman et al (1984) could not confirm this and found a significant reduction in FM in the first 16 minutes after smoking.

Alcohol administered to the mother produced no change in FM incidence (Fox et al 1978)

Ultrasound

Reports on the effect of doppler ultrasound on FM are conflicting. David et al (1975) reported that FM's were increased by 90% in controlled experiments when the fetus was exposed to doppler ultrasound. Hertz et al (1979), Phillips and Towell (1979) and Dawes et al (1981) have been unable to confirm this finding. No real-time data is available.

Labour

Fetal Movements have been studied during labour at term with real-time ultrasound. Wittman et al (1979) demonstrated that FM continue to occur episodically but did not measure their incidence. Boylan and Lewis (1980), in a mixed sample of women

ranging from early to advanced labour, found a non-significant reduction in mean values for FM. They documented a marked increase in FM with amniotomy. Richardson et al (1979), in a carefully documented longitudinal study of electively induced labour at term, found a gradual reduction in FM. The mean percentage time occupied with FM in the control period was 8,3±1,5%. This was reduced to 5,3±1,6% in the latent phase and 2,9±0,7% during active labour. The difference between the control period and active labour was significant at $p<0,01$.

Thus, as with FBM, FM are influenced by a variety of factors and are intermittent and episodic in nature. This must be taken into account when designing a biophysical test and interpreting the results.

THE CERVIX

Changes in the cervix have long been regarded as evidence of both term and preterm labour (Bishop 1964, Calder et al 1974), and have formed integral parts of scoring systems designed to predict labour outcome (Liu and Blackwell 1978). In most studies of preterm labour cervical state and change in cervical condition has played a central role in the diagnosis (Lauersen et al 1977,Wallace et al 1978, Spellacy et al 1979, Merkatz et al 1980, Creasy et al 1980, Cotton et al 1982). However, digital cervical assessment is inaccurate for prediction in early labour (Anderson and Turnbull 1969) and evidenced by the placebo effect (Anderson 1981).

The use of ultrasound for observing the cervix has recently gained popularity but for reasons other than labour. The first attempts to localise the cervix definitively using ultrasound are described by Saunders (1974) with regard to ultrasonic placentography. Since then it has become standard practice to observe the relationship between the placenta and the internal os of the cervix in describing placenta praevia (Law 1980). Visualisation of the whole cervix and cervical canal as well as the internal os is a well described technique and has found application in both obstetric and gynaecological practice. Indeed it is now considered by some to form an integral part of the assessment of cervical carcinoma (DeWet and Smit 1983).

In Obstetric practice there appear to be three clinical situations in which ultrasound of the cervix may be of benefit (Sarti et al 1979)

(1)Inevitable abortion

(2)Incompetent cervix

(3)Preterm labour

The diagnosis and subsequent management and follow-up of incompetent cervix has received most attention (Vaalamo and Kivikorski 1978, Mahran 1980, Bernstine et al 1981, Zemlyn 1981, Parulekar 1982, Vaalamo and Kivikorski 1983). These various authors have had no difficulty in visualising the whole cervix, particularly prior to 28 weeks gestation. Thereafter, when difficulty occurred it was due to the presenting part being too low or the patients inability to fill her bladder sufficiently for good resolution.

Cervical length in pregnancy is reported to vary from 3cm to a maximum of 6 or 7cm (Bernstine et al 1981, Zemlyn 1981). Vaalamo and Kivikorski (1978) found cervical shortening to be a physiological phenomenon in the mid-trimester. They documented the normal length of the cervical canal during pregnancy to be approximately 3cm (2-4cm). If it was 2cm without cervical dilatation the pregnancy continued without complication. Shortening was found to be significant by Bernstine et al (1981), and Zemlyn (1981). Jackson et al (1984) concluded that patients at risk of cervical incompetence may show progressive shortening of the cervix and benefit from continued ultrasound follow-up.

Mahran (1980) found that a diameter of the internal os of 15mm or more during the first trimester or 20mm or greater in the second to be a diagnostic parameter of cervical incompetence. Brook et al (1981) are in agreement with these findings. A 'V' shape of the internal os or herniation of the amniotic sac through the internal os into the cervical canal were thought to be the most reliable signs (Vaalamo and Kivikoski 1983, Parulekar 1982, Jackson et al 1984, Van Dongen 1984).

The use of ultrasound for assessing the cervix in preterm labour has not been systematically explored. A few case reports (Sarti et al 1979, Redford et al 1981) in advanced labour are described in the literature. No verification of the ultrasound findings were documented.

VanDongen (1984) has recently documented an important factor in ultrasonic cervical measurement. The distortion caused by bladder overdistention has been alluded to by many of the authors mentioned above. VanDongen clearly demonstrated this by measuring the cervix with an overdistended bladder, asking the patient to partially void, and then remeasuring. Not only was there considerable lengthening of the cervix but compression of a dilated internal os occurred with overdistention. This may be an important consideration when measuring the cervix in preterm labour.

From this review of the literature it is apparrent that fetal behaviour patterns alter with term labour. They are, however, influenced and affected by a number of factors which must be taken into account when designing a study using these biophysical parameters, and interpretting the results. These considerations are documented later.

In order to assess the usefulness of these parameters in the assessment and management of preterm labour, ultrasound examinations were performed on a group of women admitted to the John Radcliffe Hospital, Oxford, in apparent preterm labour. The criteria for admission to the study were

1. Less than 34 weeks gestation.
2. Contractions of more than 1 in 10 minutes frequency and

of 30 seconds or longer duration.

3. Cervix less than 4cm dilated.

4. Fetal cardiotocograph exhibiting the above contractions and a normal fetal heart pattern by the criteria of Visser and Huisjes (1977).

The incidence of treatment of uncomplicated preterm labour at the John Radcliffe Hospital is less than 10% - the majority of these patients having been transferred into the unit from elsewhere with tocolysis already initiated. It has thus been possible to study the natural course of preterm labour in the majority of patients studied.

Ethical permission was sought for the study from the local ethics committee, and granted. One hundred and twenty three women fulfilled the entry criteria and consented to be studied. A further seven patients were eligible for the study but on initial ultrasound assessment were found to have fetuses with unsuspected lethal congenital malformations and were thus excluded.

The study design and ultrasound findings will be presented and their implications for future management of preterm labour discussed.

At the time work for this thesis began data published by Chng (1981) and Sellers (1983) had recently appeared, stimulating considerable interest. Both authors demonstrated a falling neonatal death rate in infants delivered following uncomplicated spontaneous preterm labour, in comparison with the findings of Rush et al (1976) who found that in 1973 and 1974 in Oxford, this 'uncomplicated' group included 35% of all the early neonatal

deaths associated with preterm delivery. These new findings are important for they imply that patients in whom tocolytic treatment would be most appropriate may already have such good neonatal outcomes that the need for treatment could be questionable. To further elucidate this problem, as well as conducting a prospective study of women in preterm labour, I have analysed the records of all preterm deliveries in Oxford in 1981. The first chapter of this thesis presents these findings and compares them, wherever possible, with the findings of Rush et al, Chng and Sellers.

The second part of the thesis considers the physiological mechanisms which bring about the reduction in FBM with the onset of labour. Recent observations in fetal lambs suggest that increasing levels of prostaglandin E in the fetal circulation may be the factor responsible.

Regulation of FBM is central and the area seems to be situated in the brain stem in the region of the pons (Dawes 1984). This regulation is complex and, as yet, not fully defined. Marked differences exist between the responses of the fetus in utero and the infant after birth; the most striking being in the effect of hypoxia. While hypoxia in the neonate causes hyperventilation, intrauterine hypoxia causes arrest of FBM from central inhibition (Dawes 1984). This central inhibition may be the mechanism by which increased fetal prostaglandin E levels reduce FBM during labour.

Prostaglandins of the E and F type are powerful oxytocics and appear to play a major role in the labour process in both animals (Thorburn and Challis 1979) and man (Embrey 1969). As

has been documented earlier, Kitterman et al (1979, 1980) found that intravenous infusion of prostaglandin synthetase inhibitors (PGSI) eg.Indomethacin and Meclofenamate, into fetal lambs near term caused prolonged vigorous FBM lasting many hours, during either low or high voltage electrocortical activity. ECOG activity and blood gas values remained unchanged. Conversely, infusion of prostaglandin E2 arrested FBM. These findings have been confirmed by Koos (1982) and Dawes et al (1983). Koos demonstrated that similar effects could be achieved using lower doses of PGSI given intravenously and also showed that Meclofenamate perfused into the fetal cerebrospinal fluid space in small doses causes prolonged, continuous FBM. The site of action is central in the medulla, as the effects persist following bilateral section of the vagi and carotid nerves (Dawes 1984) and can be demonstrated after pontine section of the brain stem in fetal lambs (Koos 1982). Recent observations by Patrick et al (1981b), that FBM return to normal in 12 hours in spite of continuous infusion of PGSI suggests that the action of prostaglandin in the medulla may not be directly on the control mechanism, but due to local, eg. circulatory effects.

Further evidence supports the role of prostaglandins. In sheep, fetal plasma concentration of prostaglandin E2 (PGE2) is elevated towards the onset of labour (Mitchell et al 1980). For obvious practical and ethical reasons, similar data is not available in man. However, the level of PGE in fetal plasma increases in labour (Bibby et al 1979), apparently coming from the placenta since the concentration is higher in umbilical venous than arterial plasma. The fact that administration of PGE can be used to maintain ductal patency in neonates with certain

types of congenital heart disease (Elliot et al 1975, Olley et al 1976) provides associated evidence of prostaglandin effects, because a reported complication of this PGE treatment is intermittent neonatal apnoea (Olley et al 1976).

To investigate the relationship between PGE and FBM in man I have investigated the effects on FBM of PGE2 administered vaginally to bring about cervical ripening and induction of labour, in patients with normal pregnancies at term. The effect of PGSI drugs was not studied of course, as they could cause premature closure of the ductus arteriosis in utero, leading to fetal death or persistent pulmonary hypertension of the newborn (Wilkinson et al 1979).

MacKenzie et al (1980a) working in the Nuffield Department of Obstetrics and Gynaecology in Oxford, demonstrated a significantly higher level of PGE in the umbilical cord plasma of women whose labour was induced by PGE2 pessaries than in those whose labour had been induced by amniotomy and oxytocin, suggesting that the prostaglandin had been directly transferred to the fetus. I have investigated the maternal absorption patterns of PGE following its vaginal administration to document how the levels of PGE change with time in the mothers circulation after vaginal administration of PGE. Using fetoscopy, I have investigated transfer of PGE to the fetus in the second trimester by direct sampling of fetal blood. Using real-time ultrasound and an on-line computerised event-marker system I have investigated the effect on FBM at term of maternal vaginal administration of PGE2.

Throughout this thesis I have attempted to draw attention to the clinical implications and applications of my findings.

PART I

CHAPTER 1.

THE TRENDS IN PRETERM DELIVERY

To examine trends in preterm delivery a retrospective study has been carried out, of 403 women admitted in preterm labour or electively delivered preterm in the John Radcliffe Hospital, Oxford, in 1981. Preterm labour was defined as labour occurring spontaneously before 37 completed weeks of pregnancy. The lower limit of gestation for inclusion in this analysis was 22 weeks or 500gm birthweight. Gestational age was calculated from the first day of the last menstrual period. When the dates were uncertain gestational age was estimated using ultrasonic scan measurements combined with paediatric assessment at birth using the criteria of Farr et al (1966). For comparison with the other studies preterm labour was diagnosed if the patient was admitted with regular painfull contractions or spontaneous rupture of the fetal membranes.

During 1981 a total of 5905 women were delivered at the John Radcliffe Hospital. There were 5843 singleton and 62 multiple pregnancies (58 sets of twins, 3 sets of triplets and 1 set of quadruplets). The records of the 403 women admitted in preterm labour or delivered electively preterm could all be studied in detail. Of these 403 patients, 226 (56%) were admitted in spontaneous preterm labour and delivered preterm, 90 (22,3%) were delivered electively preterm and 87 (21,7%) were admitted in preterm labour but finally delivered after 37 weeks gestation. A total of 316 women, therefore, delivered too early in gestation and between them they delivered 345 preterm infants (292 singletons, 20 sets of twins, 3 sets of triplets and 1 set of quadruplets). Hence the overall incidence of preterm delivery in this population was 5,78%. Table 1 compares this population with the studies of Rush et al, Chng and Sellers.

TABLE 1.

THE PRETERM LABOUR POPULATION

STUDY	No.(and %) spont PTD	No.(and %) elect.PTD	No.(and %)PTL going to term	Incidence PTD
Rush 1973-4	284(72%)	109(28%)	-	5,1%
Chng 1975	65(65%)	34(34%)	23(23%)	5,0%
Sellers 1979	219(82,3%)	47(17,7%)	75(22%)	5,2%
Castle 1981	226(71,5%)	90(28,5%)	87(21,7%) *	5,78%

* - % of total preterm labour population.

PTD - Preterm Delivery

PTL - Preterm Labour

All other percentages are of the total delivered.

The perinatal mortality rate for this preterm group was 86,5/1000 births which was 30 times that for term deliveries (2,84/1000 births). These results are shown in table 2 and compared with the other series mentioned.

Seventeen stillbirths occurred before the 37th week of pregnancy and accounted for 65% of all stillbirths in 1981. All of these preterm stillbirths occurred before the onset of labour. Six were associated with abruptio placentae, four had lethal congenital abnormalities, four were due to intrauterine asphyxia associated with intrauterine growth retardation and placental infarction, one was caused by cord entanglement and two were of unknown cause.

Of the 9 early neonatal deaths (ENND) not due to lethal congenital abnormality, 8 (89%) occurred in infants with a gestational age of less than 37 weeks (table 2) giving a preterm early neonatal death rate in these "normal" infants of 24,4/1000 births, in contrast to a rate of 0,18/1000 if delivered at 37 weeks or more.

Multiple pregnancy

Multiple pregnancy is associated with a far higher incidence of preterm delivery (table 3). Although these women comprise only 7,6% of those delivered preterm a significant proportion of the ENND's occur in this group. This situation remains unaltered. What has altered, however, is the infant survival with a corrected perinatal mortality rate (PMR) of 39,2/1000, which contrasts very favourably with previous years. The two ENND's were in very sick preterm infants. One was a 25 week baby weighing 600gm with an abruptio placenta leading to delivery of a stillborn infant and this hypoxic, acidotic neonate of extreme

TABLE 2.

Database	Gest.age	No	SB's	ENND(Excl. lethal anom)	ENND due to lethal anomaly
Oxford 1973-4	<37	486	50	34(85%)	7
	>37		35	6	16
Oxford 1979	<37	292	9	20(77%)	3
	>37		20	6	7
Oxford 1981	<37	345	17	8(89%)	5
	>37		9	1	6

Preterm PMR Oxford	1973-4	95,3/1000
	1979	109/1000
	1981	86,5/1000

TABLE 3

MULTIPLE PREGNANCY

YEAR	NUMBER (% PTD)	INCIDENCE (OF PTD)	%ENND (NO.)	PMR
1973-4	40(10%)	47%	27%	118,4/1000
1979	24(10%)	38%	20%(4)	166/1000
1981	24(15,4%)	38,7%	25%(2)	39,2/1000

prematurity. The infant suffered a cardiorespiratory collapse shortly after delivery and was not resuscitatable. The second death occurred in a pregnancy complicated by premature rupture of the membranes with infection. The neonate was septicaemic and died from asphyxia and pulmonary complications. This baby delivered at 29 weeks gestation and weighed 1340gm.

Complicated Spontaneous preterm labour (Singleton)

Spontaneous preterm labour associated with fetal growth retardation or maternal complications accounted for 32,5% of singleton preterm deliveries (Table 4). Antepartum haemorrhage was the most common complication (63%) which continues the trend evident in the earlier series of Rush and Sellers. The PMR (22.2/1000) again shows a marked reduction compared with previous years (135/1000 in 1979 and 104.2/1000 in 1973-4) in Oxford and 316/1000 in Aberdeen in 1975. The two neonates that died were both associated with antepartum haemorrhage. One was a 27 week, 730gm infant and one a 30 week, 2kg baby. Both were delivered in a very shocked and acidotic condition.

Elective delivery

Deliberate obstetric intervention occurred in 70 women, accounting for 25,3% of singleton preterm deliveries, which remains a relatively unchanged incidence (table 5). The proportion of ENND's attributable to this group is high (66%) but in real terms represents 4 of only 6 ENND's in total. The PMR has steadily risen from 1973 to 1981. This may represent an increasing tendency to deliver very preterm and compromised fetuses in the hope of salvage. Of the four ENND's, two were associated with severe abruptio placentae (one the result of

TABLE 4

COMPLICATED PRETERM LABOUR

Database	No.and % PTD	ENND No. and %	PMR
Oxford 1973-4	96 (27,2%)	10 (29%)	104,2/1000
Aberdeen 1975	19 (21,1%)	6 (55,7%)	316/1000
Oxford 1979	96 (41,5%)	13 (81,2%)	135/1000
Oxford 1981	90 (32,5%)	2 (33%)	22,2/1000

TABLE 5

ELECTIVE DELIVERY

Database	No.and % PTD	ENND No.and %	PMR
Oxford 1973-4	109 (30,9%)	3 (9%)	27,5/1000
Aberdeen 1975	28 (31,1%)	1 (44,3%)	36/1000
Oxford 1979	42 (18,2%)	2 (12,5%)	48/1000
Oxford 1981	70 (25,3%)	4 (66%)	57,1/1000

abdominal trauma suffered in a road traffic accident). One was a very growth retarded infant of 600gm delivered at 27+ weeks gestation to a woman suffering from severe pre-eclampsia. This babe died from complications of hyaline membrane disease. The fourth death resulted from severe rhesus isoimmunisation in a hydropic 33 week neonate who exhibited myocardial ischaemia at birth and died during an exchange transfusion.

Uncomplicated Unexplained preterm labour

As seen in table 6 the incidence of this group remains very constant at just over 40%. There has been a startling reduction in the PMR in Oxford from 1973-4 (81/1000) to 1979 (10,8/1000) and 1981 when there were no deaths. This good outcome mirrors that found in Aberdeen on a small number of patients.

DISCUSSION

The trend in preterm delivery is for greater infant survival in all groups apart from elective delivery. A greater proportion of preterm deaths are attributable to stillbirths and lethal congenital anomalies (73% in 1981,37% in 1979 and 62% in 1973-4). The number of "normal" infants born alive that subsequently demise is so small that percentage analysis is unhelpful.

From table 1 the incidence of preterm delivery has risen slightly which may be due to transfers into the unit. The ratio of spontaneous to elective delivery and the incidence of non-progressive preterm labour has remained unchanged between 1973 and 1981 in Oxford.

Table 7 demonstrates the early neonatal mortality for preterm births of singleton infants delivered alive, and without lethal deformity in Oxford in the three series and in Aberdeen in

TABLE 6

UNCOMPLICATED PRETERM LABOUR

YEAR	1973 - 4	1975	1979	1981
No. & %	148 (42)	43 (47,8)	93 (40)	117 (42,2)
ENND	12	0	1	0
% ENND	35	0	6,2	0
PMR	81/1000 *	0	10,8/1000	0

* No infant <28 weeks or <1250gm survived and 8 of the 12 (75%) were in this category.

1975. This table also illustrates the part played by antepartum haemorrhage (APH) which has pride of place in association with ENND. Fetal growth retardation with placental infarcts follows APH in association with ENND and prompts speculation that causation may be related to abnormalities of placentation.

Zlatnik (1972) and Fuchs (1976) have pointed out that only a small proportion of preterm labours are eligible for tocolytic therapy. This is confirmed by both the Oxford 1979 and 1981 data where 17% and 12% respectively of the women were potentially treatable by current criteria. Stubblefield (1984) has recently suggested that these criteria should be broadened to include women with ruptured membranes and those in advanced labour if we are to improve outcome. This view, however, is not supported by this data.

Survival is now the norm in the spontaneous preterm labour of unknown cause. This is in no small measure due to the advances in neonatal intensive care over the past 10 years. However, in analysing this data it is interesting to note the lack of extreme prematurity in this group. Rush et al in 1973-4 documented 8 of 12 ENND in this group to be less than 28 weeks gestation. In Aberdeen in 1975 there were no infants delivered before 28 weeks in this category. The Oxford 1979 data shows 1 birth pre-28 weeks (a 23 week gestation) and a further 5 pre-34 weeks gestation. In 1981 in Oxford, of 117 infants in this group only 1 was under 28 weeks gestation. One fell in the 30-32 week bracket, 7 in the 32-34 week group and the rest were over 34 weeks gestation. There were no ENND's. This may indicate a greater awareness of, and more dilligent search for, the cause of preterm labour than in the past, thus putting the very preterm

TABLE 7

ENND for singleton infants delivered alive and without lethal deformity

Database	Incidence PTB	No.PTB	ENND	APH	Mortality per 1000 PTB
Oxford 1973-4	5,1	353	25	6(24%)	70,8
Aberdeen 1975	5,0	90	7	4(57%)	77,7
Oxford 1979	5,2	231	16	12(75%)	69,3
Oxford 1981	5,78	277	6	4(67%)	21,7

TABLE 8

Short-term morbidity

Intact membranes

n=36

No.admitted to neonatal ICU. 14 (39%)

Total time - 171 days (mean 12,2±11,4 days)

Morbidity - 1 neonatal convulsion ?cause

2 apnoeic attacks

4 phototherapy (no exchanges)

Ruptured membranes

n=81

No.admitted to neonatal ICU. 33 (40,7%)

Total time - 702 days (mean 25±24,7 days)

Morbidity - 10 Transient tachypnoeas

1 Septicaemia

4 Respiratory distress with ventilation (mean 3 days)

6 Phototherapy (no exchanges)

3 Patent Ductus Arteriosus of which

1-ligated

1-Treated with Indocid

1-Spontaneously closed

Long-term morbidity

1 - Birth asphyxia in a 34 week infant which weighed 3,89kg after difficult forceps. Severe HMD,Convulsions and hypotonia.Residual neurological deficit

neonate into other groups. Should this trend continue then a more aggressive policy of treatment, and indeed any treatment at all, may be inappropriate.

Before advocating a drastic reappraisal of therapy it is necessary to examine outcome more carefully. Early neonatal mortality is a crude assessment and the morbidity of the survivors, both short and long-term, is of paramount importance. To investigate this the incidence of admission to the neonatal intensive care nursery and morbidity during admission and, if documented, following discharge have been studied. Table 8 documents this information.

In the group eligible for treatment, ie. those with intact membranes, 14 (39%) went to the neonatal intensive care nursery (ICU) for a total of 171 days. They suffered no significant morbidity. In those women admitted with ruptured membranes in labour from an unknown cause 33 (40,7%) went to the neonatal ICU for a total of 702 days (one 25 week infant of 810gm being admitted for 142 days). The morbidity was as documented with one long-term sequela of neurological deficit. This followed birth asphyxia at delivery by forceps of a 34 week infant weighing 3,89kg (>90%ile). The baby suffered severe hyaline membrane disease (HMD), experienced convulsions and was hypotonic. This may have been an undiagnosed diabetic pregnancy.

There were four late neonatal deaths in Oxford in 1979 and 1981 (two in each year). One patient, a 25 week infant, died at 53 days of necrotising enterocolitis after a spontaneous uncomplicated labour. The other three were following elective delivery or consequent on complicated preterm labour.

Based on this data the following conclusions may be drawn.

(1)The incidence of preterm delivery remains unchanged.

(2)The proportions of elective delivery, complicated delivery and uncomplicated preterm labour show no significant change.

(3)In all groups except elective delivery infant survival has improved.

(4)The major threat to the preterm neonates survival continues to be posed by antepartum haemorrhage.

(5)Infant survival and both short-and-long term morbidity may, at best, be only marginally improved by a totally effective tocolytic regime in those patients with unexplained, uncomplicated preterm labour.

(6)The economic costs of intensive care for preterm infants born following unexplained preterm labour remains high.

Until it can be established conclusively that this trend in the outcome of uncomplicated unexplained preterm labour continues both nationally and internationally it remains imperative that we establish firm diagnostic criteria for preterm labour progressing to preterm delivery.

CHAPTER 2

FETAL BREATHING MOVEMENT AND PRETERM LABOUR

It has been established that fetal breathing movements (FBM) are altered by changes in the fetal enviroment. As indicated in the introduction, studies of FBM in both spontaneous and induced labour at term, have demonstrated a reduction in FBM to insignificant levels (Boddy et al 1974b, Wittman et al 1979, Richardson et al 1979, Boylan and Lewis 1980). To investigate whether a similar reduction in FBM occurs in preterm labour and, if so, whether this will predict those women progressing to preterm delivery, ultrasound examinations were performed on patients in preterm labour.

Patients and Methods

One hundred and twenty three patients were admitted to the study after fulfilling the entry criteria documented earlier. Informed verbal consent was obtained from all patients and the following relevant information noted:-

Reason for admission (contractions ± antepartum haemorrhage or ruptured membranes)

Time of day

Recent medication

Recent alcohol ingestion

Recent cigarette smoking

In order to utilise a biophysical phenomenon as a clinical test in the acute admission situation of a delivery suite the test must fulfill certain requirements. These are:-

(1) Be easy to perform by on-call staff.

(2) Be as unambiguous as possible.

(3) Utilise simple existing equipment.

(4) Be performed within a time limit that is practical.

In setting up this study the above points were addressed.

Real-time ultrasonography of the basic standard required to visualise FBM, FM, assess liquor volume, measure fetal parameters of biparietal diameter, abdominal circumference and femur length and localise the placenta, is well within the scope of senior midwives and obstetricians. This requires only basic training and practice.

To fulfill the criterion of being unambiguous so making interpretation easy, an "all-or-none" approach has been adopted. From the review of the literature it becomes clear that, although many factors influence the incidence of FBM, apart from hypoxia and general anaesthesia, they do not abolish it. Many authors on FBM advocate increasing sophistication in the recording of breath-to-breath intervals and analysis of breathing amplitude (eg.Marsal 1983), and preach caution in drawing conclusions regarding fetal status from FBM incidence (Patrick 1982). The variable and episodic nature of this phenomenon with its large inter-and-intra-fetal variations lends support to this. However, for the test to be realistically practicable, very sophisticated techniques and machinery cannot be contemplated. I have thus adopted the opposite approach of the "all or none" concept for interpretation of FBM, and carefully defined this. Manning and Platt in 1980 also utilised this concept when using biophysical parameters to assess fetal well-being and found it effective. This enables a small, portable and inexpensive real-time ultrasound machine to be used.

In the United Kingdom few, if any, obstetricians advocate tocolytic therapy after 34 weeks gestation. The perinatal morbidity and mortality rises sharply prior to this gestation and it is to this group of preterm labourers that I have addressed

myself. Using Patrick's data on fetal apnoea, between 1 and 1,5% of normal fetuses at 33 weeks may be expected to show no FBM within 60 minutes. At 30 weeks gestation fewer than 0,5% of normal fetuses remain apnoeic for 60 minutes or longer. The false positive aspect of the test should thus be minimal. The time limit of 60 minutes was chosen as it was felt a test taking longer would be impractical in the delivery suite situation.

FBM was defined as "present" if sustained for 20 seconds or longer, whereupon the test was discontinued, and "absent" if no sustained FBM was visualised over 60 minutes. From Wittman et al's work (1979) fetuses at term were noted to have episodes of FBM in labour lasting up to 30 seconds. As noted earlier, gestation alters the pattern (not incidence) of FBM and at earlier gestations it is more rapid and the episodes are of shorter duration (Roberts et al 1980a, Trudinger et al 1980). It was thus decided to make the cut-off 20 seconds to allow for possible gestation differences.

The method used for recording FBM was a simple event-marker system. This comprised a tachometer attached to a clipboard which could be activated with one hand and visualised while observing the ultrasound screen. Apnoea, as defined by Patrick et al (1980a), was any breath-to-breath interval of 6 seconds or more. On observing the initiation of FBM the tachometer was activated. At the last breath 5 seconds were allowed to elapse before stopping it to ensure that no further FBM took place. The length of FBM interval was then read off. This simple system proved effective and easy to use.

The patients admitted to the study were divided into four groups.

Group A - Singleton fetus with intact membranes and contractions.

Group B - Singleton fetus with spontaneous rupture of the membranes and contractions.

Group C - Singleton fetus with antepartum haemorrhage and contractions.

Group D - Multiple pregnancy.

CHAPTER 2-1

SINGLETON FETUS WITH INTACT MEMBRANES AND CONTRACTIONS ONLY

Following the selection criteria as outlined earlier, 60 patients were admitted to the study in this group. These patients all presented with normal singleton pregnancies, intact membranes, no vaginal bleeding and complaining of painfull uterine contractions only. None showed evidence of any infection. They were then scanned for FBM which was documented as simply "present" or "absent" by defined criteria. Following the scan maternal peripheral venous blood was taken into Ethylene Diamine Tetra Acetic acid (EDTA) for a full blood count and Sodium Fluoride for a random blood sugar.

Results

From table 9, 43 patients continued in pregnancy for more than a week in whom 42 fetuses exhibited FBM and 1 did not. Seventeen patients delivered within 1 week in whom only 7 fetuses exhibited FBM. In those 11 patients where FBM was absent, 10 delivered within 1 week. Thus the absence of FBM was significantly ($p<0,001$) related to delivery within a week, whereas the presence of FBM predicted continuing pregnancy.

The predictive power of the test was measured as its ability to predict preterm delivery within a week of the scan. This was felt appropriate as patients in early labour who may take over 24 hours to establish and deliver would be included as test failures. This would also apply to women who continued to contract on and off after admission and delivered within a week. Statistical analyses were performed using the X^2 test with Yeats correction.

TABLE 9

FBM and Outcome of preterm labour in singleton pregnancies with intact membranes and contractions only

OUTCOME	FBM PRESENT	FBM ABSENT	TOTAL
CONTINUED >1 WEEK	42	1	43
CONTINUED <1 WEEK	7	10	17
TOTAL	49	11	60

$X^2 = 22,3 - p<0,001$

Discussion

From the introduction many factors affect FBM in man. In order to minimise the possibility of a reduction/cessation of FBM being due to causes other than labour as many of these factors as possible were examined.

The time of day as indicated by Patrick et al (1978a) and Roberts et al (1979) significantly effects the incidence of FBM. In this group of 60 patients, 37 (62%) were admitted between the hours of 8pm and 8am, and 23 (38%) between 8am and 8pm. Seventeen patients delivered within a week of which 9 were scanned between 8pm and 8am and the remaining 8 between 8am and 8pm (table 10). There was no difference in the number or distribution in the two groups and thus time of day could not have influenced the findings - specifically these false negative results.

Maternal plasma glucose concentrations were measured at time of scan (table 11). These results show no significant difference in maternal plasma glucose between those pregnancies exhibiting FBM and those not.

No patient had consumed alcohol within 3 hours of admission and only 2 patients had smoked a cigarette within 3 hours of admission to the hospital. Both fetuses of the patients who had smoked exhibited FBM and the pregnancies continued. No patient was taking medication. Thus the groups of breathing and non-breathing fetuses were comparable with regard to these factors.

In preterm labour with intact membranes, no bleeding and a singleton pregnancy, the presence of FBM seems to indicate that pregnancy will continue while absence of FBM foreshadows early delivery. This is not invariably so and scrutiny of the test failures is necessary.

TABLE 10

FBM, TIME OF DAY AND DELIVERY

TIME OF DAY	FBM PRESENT	FBM ABSENT	TOTAL
8pm to 8am	4	5	9
8am to 8pm	3	5	8
TOTAL	7	10	17

TABLE 11

Relationship between maternal plasma glucose concentration and FBM

FBM -ve	FBM +ve
n = 11	n = 49
5,1 ± 1,18mmol/l	4,55 ± 1,1mmol/l

In this group of 60 patients the test falsely predicted the outcome in 8 patients, 7 of whom had FBM. Where FBM was present but delivery occurred, 3 had hydramnios (defined as liquor pools >10cm by 10cm on ultrasound), 2 were subsequently found to have chorioamnionitis (in spite of intact membranes), and one patient had a concealed accidental haemorrhage and delivered 4 days post scan. The retroplacental clot had not been seen on the scan. The seventh patient had a cervical suture in situ and at scan the internal os was seen to be cone shaped and 3cm dilated. The suture was removed as it was felt by the on-call staff that cervical damage was imminent. The patient delivered 30 minutes later. In the case where FBM was absent but pregnancy continued it was later ascertained that the patient was 36 weeks pregnant at the time of the scan with a small baby and uncertain dates. Apnoea of 60 minutes at this gestation occurs in 5-6% of normal pregnancies.

It is tempting to speculate that the trigger(s) for labour in these cases (excess uterine volume, concealed haemorrhage, cervical incompetence and infection) may differ from spontaneous labour and that the physiological reduction in FBM seen in the other fetuses is modified or delayed. In the patient with the retroplacental clot the diagnosis was made following delivery. She has been included in this group as, on admission, she would have been classified as "uncomplicated" and eligible for treatment.

As treatment with tocolytics may modify the timing of delivery and thus have affected the results in favour of FBM as a predictor this matter has been addressed. The study was not designed to assess treatment efficacy but, as treatment was given

TABLE 12

FBM, TREATMENT WITH INTRAVENOUS β-MIMETICS AND OUTCOME

FBM ABSENT

OUTCOME	TREATED	NOT TREATED	TOTAL
Continued >1week	0	1	1
Continued <1week	5	5	10
Total	5	6	11

p- not significant

FBM PRESENT

OUTCOME	TREATED	NOT TREATED	TOTAL
Continued >1week	8	34	42
Continued <1week	4	3	7
Total	12	37	49

X^2 = 2,87 - p-not significant

to some patients, the possibility of this altering the results arises. Of the 60 patients, 17 (28%) received tocolytic therapy in the form of intravenous Ritodrine or Terbutaline following the ultrasound examination for FBM. Only 2 patients were on treatment at the time the scan was performed. One patient exhibited FBM and the other did not; both went on to deliver within a week.

This is a higher incidence of treatment than earlier estimated (15 of 58 (26%) of patients booked at the John Radcliffe Hospital). It is disproportionate to the overall rate of treatment during the duration of the study (9,8%). The reason for this difference is unknown as the FBM status was not revealed to the on-call staff. It is possible that the interest in the pathology may have resulted in closer observation by the staff resulting in more treatment being administered. From table 12 it may be concluded, however, that treatment did not appear to alter the FBM predictions significantly. Where FBM was absent delivery occurred regardless of whether treatment was given or not. Where FBM was present (those where labour would be expected to spontaneously subside) 4 patients delivered in spite of treatment. It is not possible to speculate whether any of the 8 patients with FBM who were treated and where pregnancy continued would have delivered had treatment not been given.

To assess the performance of FBM in the prediction of labour outcome against traditional parameters, contractions and cervical findings (clinical) were analysed. This was to ensure that the diagnosis was not obvious from these two parameters thus making the observation for FBM unnecessary. Contractions measured by external tocography give no indication of co-ordination of the

TABLE 13

CONTRACTIONS AND OUTCOME

(n = 48)

OUTCOME	DURATION (SECONDS)	FREQUENCY
Continued >1week	51,5 ± 9,6sec	2,97 ± 1 contrn./ 10min.
Continued <1week	46,4 ± 9,5sec	2,77 ± 0,77 contrn/ 10min.

TABLE 14

CERVICAL STATE AND OUTCOME

(n = 60)

OUTCOME	DILATATION	LENGTH
Continued >1week	1,78 ± 0,93cm	1,45 ± 0,6cm
Continued <1week	2,37 ± 0,88cm	1,22 ± 1,1cm

Student t test = 1,356 p-not significant

myometrial activity nor intrauterine pressures generated. A crude assessment, and the only one available to the clinitian, is the duration and frequency of contractions on the external tocograph. In this group 48 (80%) of tocograph traces were considered to be adequate for interpretation (ie. of 30 minutes duration and sufficiently good quality to easily define a contraction's beginning and end from the baseline). There was no statistical difference in either duration or frequency of contractions in those patients where labour subsided and those progressing to delivery (Table 13).

The cervical findings at vaginal examination in these patients also gave no indication of whether delivery was imminent or not. The cervical measurements in those patients progressing to delivery showed a tendency to greater dilatation and shortening but this was not significant (Table 14).

The findings confirm the observations made in the introduction that these parameters are unreliable. In contrast, FBM will distinguish the majority of women in early preterm labour progressing to delivery within a week. The implications for the future management of preterm labour will be discussed following the findings of the other 3 groups.

CHAPTER 2 - 2

SPONTANEOUS RUPTURE OF THE MEMBRANES (SROM) AND CONTRACTIONS

There is conflicting data regarding FBM and artificial rupture of the membranes prior to labour as documented in the introduction. No data regarding FBM with SROM is available and this question has not been systematically addressed. It is likely that SROM precedes the onset of labour in a high proportion of preterm deliveries. Gillibrand (1967) found SROM to precede preterm labour in 38% of singleton pregnancies delivered at less than 34 weeks gestation. The duration of pregnancy affected the interval between SROM and the onset of labour and delivery. The earlier in gestation the membranes ruptured the longer the interval to delivery. In 26% of patients in whom the membranes ruptured before the 34th week, labour had not started within a week. Brassard et al (1981) found that SROM preceded spontaneous preterm labour leading to delivery in 47% of cases analysed (n = 301). This greatly exceeds that reported for all pregnancies of 6 - 15% (Turnbull et al 1983). Turnbull et al (1983), however, documented that in spite of preterm SROM, 15% of these pregnancies went on to deliver beyond 37 weeks gestation.

Patients and Methods

Twenty eight patients were admitted to the study in this group. They all had normal singleton pregnancies and had experienced spontaneous membrane rupture proven by observation on admission and/or an unequivocally positive Nitrazine test (Amnicator - Medical Wire and Equip. Co. Ltd. Corsham U.K.). No patient had clinical evidence of infection on admission and none had experienced bleeding. An ultrasound scan for FBM was performed as detailed earlier. Thereafter careful note was made

TABLE 15

SPONTANEOUS RUPTURE OF MEMBRANES, FBM and OUTCOME

OUTCOME	FBM present	FBM absent	Total
Continued > 1 week	2	0	2
Delivered < 1 week	14	12	26
Total	16	12	28

$X^2 = 0,28$ - p - not significant

of the quantity of liquor remaining in the uterus and the largest pool was measured. Blood was taken into EDTA for a full blood count, and Sodium Fluoride for random blood sugar estimation.

Results

Table 15 documents the FBM findings with relation to SROM. In contrast to those pregnancies with intact membranes, FBM status bears no relationship to delivery once the membranes have ruptured. It is clear from the table that whether FBM is present or not delivery will occur within 1 week in most patients. In the 2 patients continuing beyond a week both fetuses showed FBM. These pregnancies continued, in spite of bouts of contractions and further leakage of liquor, for 41 and 48 days respectively. Multiple repeated scans at 48 hour intervals showed the fetuses to have FBM until 24 to 36 hours before delivery. At this stage FBM was considered absent by the defined criteria.

Discussion

As in chapter 2 - 2 it is necessary to ensure that no external influences known to effect FBM have altered the findings. Tables 16 and 17 show the distribution for time of day and the relationship between FBM and maternal plasma glucose concentration. There is no significant difference in these factors when FBM is present or absent. Eight of the women were smokers (seven of them smoking >10 cigarettes/day). Five had smoked a cigarette within 3 hours of admission. Of these 5, 3 fetuses were apnoeic and 2 had FBM. It is thus unlikely that FBM status was effected by smoking. No patient had consumed alcohol and none were on medication.

The difference between the outcome of labour relative to FBM in those women with intact membranes and those where SROM has

TABLE 16

FBM and TIME OF DAY

Time of day	FBM present	FBM absent	Total
8pm - 8am	5	1	6
8am - 8pm	11	11	22
Total	16	12	28

$X^2 = 0,99$ $p < 0,5$ not significant

TABLE 17

Relationship between Maternal Plasma Glucose Concentration and FBM

FBM absent	FBM present
n = 12	n = 16
4,2 ± 0,56 mmol/l	4,7 ± 1,13 mmol/l

p - not significant

occurred is remarkable. Certainly spontaneous membrane rupture does not inhibit FBM and may quite possibly stimulate it. The mechanisms for this and why labour does not suppress FBM as seen in the previous chapter are unknown. Clearly use of the presence or absence of FBM on admission as a predictor of labour outcome is of no value.

Measurement of liquor volume has proved useful. Hobbins et al (1979) documented a 7% incidence of oligohydramnios unassociated with congenital malformation. This was caused by intrauterine growth retardation (IUGR), premature rupture of the membranes and postmaturity in their series. Manning et al (1981b) utilized oligohydramnios to detect IUGR in high risk pregnancies and claimed an 83% success. They defined oligohydramnios as where the largest pool of liquor measured less than 1cm in largest diameter. More recently, Philipson et al (1983) and Hill et al (1983) have found this index to be less sensitive. The time interval between scan and delivery was long (average 2 weeks) and the decrease in liquor could have ocurred in the interim. The incidence of oligohydramnios within a normal (low-risk) population has been noted to be 0,43% (Hill et al 1983) and 3,9% (Hoddick et al 1984) and probably depends on the incidence of IUGR in a given population. The definitions vary. Manning et al (1981b) used the < 1cm rule whereas Hobbins (1979) and Hoddick et al (1984) did not measure the liquor pools but relied on crowding of the fetal parts and a poor fluid/fetal interface. In the study group of patients it was found that in all cases where the largest pool of liquor measured less than 2cm in greatest diameter crowding of the fetal parts and poor fluid/fetal interface was invariable.

TABLE 18

LIQUOR VOLUME AND DELIVERY

OUTCOME	NORMAL LIQUOR VOL.	DECREASED LIQUOR	TOTAL
Delivered >48hr	5	1	6
Delivered <48hr	2	20	22
Total	7	21	28

$X^2 = 10,18 \quad p < 0.01$

Of the 28 patients in this group 7 were considered to have normal liquor volume. Five of these 7 pregnancies continued for more than 48 hours, whereas only 1 of 22 patients with oligohydramnios did so. This is statistically highly significant (See table 18). Repeated scans at 48 hour intervals were performed on those women who remained undelivered. Contractions had ceased in 3 of these 6 patients. At subsequent scans decreased liquor volume heralded delivery within 48 hours.

All fetuses progressing beyond 48 hours showed FBM at the initial scan. At subsequent scan, prior to delivery within 48 hours, none of these 6 evidenced FBM. Thus, should delivery not occur within 48 hours in the presence of ruptured membranes, observation of liquor volume and FBM reliably predict the onset of labour. In the clinical situation this information may be of value should the administration of steroids for pulmonary maturation be contemplated.

CHAPTER 2 - 3

ANTEPARTUM HAEMORRHAGE (APH) AND CONTRACTIONS

From the data presented in chapter 1 it is clear that APH poses a major threat to the preterm infant's survival. FBM are abolished by hypoxia in experimental animals and this finding has been used to assess fetal well-being in high-risk pregnancy. Trudinger et al (1978), studying a group of high-risk patients which included patients with APH, documented reduced FBM in these fetuses. They concluded that FBM was valuable in the antenatal assessment of fetal well-being and was a sensitive and early indicator of fetal compromise. Marsal (1978) examined 100 consecutive pregnancies and found that 24 women with various disorders of pregnancy (including APH) had a significantly higher proportion of fetuses with low incidence of FBM or apnoea. However, there was no correlation between the FBM incidence and subsequent course of pregnancy. A recent case report (Hill et al 1984) documents FBM as being present concommitant with an abruptio placenta within hours of progressive labour.

To date no study formally examining the relationship between FBM or fetal biophysical profiles and APH either antenatally or during labour has been published. This is necessary considering the hazardous nature of the pathology.

Patients and Methods

Twenty four patients with APH and contractions were admitted to the study. All exhibited normal fetal heart patterns as defined by Visser and Huisjes (1977), thus eliminating as far as possible the risk of hypoxia being a complicating factor in analysing FBM. A scan to detect FBM was performed and thereafter a careful assessment of the placenta was made.

TABLE 19

ANTEPARTUM HAEMORRHAGE, FBM and OUTCOME OF LABOUR

OUTCOME	FBM present	FBM absent	Total
Continued > 1 week	11	1	12
Delivered < 1 week	5	7	12
Total	16	8	24

$X^2 = 4,7 \quad 0,02 < p < 0,05$

Results

The relationship between FBM and labour outcome in preterm labour complicated by APH is seen in table 19. In the 16 patients where FBM was present, only 5 went on to deliver within a week of scan. Where FBM was absent 7 of the 8 patients delivered within a week. FBM thus correlated significantly with labour outcome. Bleeding was caused by accidental haemorrhage (abruptio) in 14, placenta praevia in 2, and no cause was found in 8. In 9 of the 16 where placental pathology was confirmed, this pathology was diagnosed on scan (2 placenta praevias and 7 abruptio placentae). A detection rate of 56%.

Discussion

As in the previous categories, factors known to effect FBM have been assessed. From tables 20 and 21 it is apparent that neither time of day nor the maternal plasma glucose concentration influenced the FBM status.

Seven of the 24 women were smokers but only 1 had smoked a cigarette within 3 hours of admission. This fetus exhibited FBM and the pregnancy continued. No patient had imbibed alcohol before admission and none were taking medication.

As with uncomplicated singleton preterm labour with intact membranes (chapter 2 - 2), FBM in association with APH and contractions seems to indicate that pregnancy will continue, whereas absence of FBM predicts delivery. The test, however, recorded 6 false predictions. Of the 5 patients where FBM was present but delivery occurred within a week, 4 suffered recurrent abruptions of the placenta following the initial examination. The fifth patient was a complicated case of previous multiple abdominal surgery who continued to bleed vaginally and

TABLE 20

TIME OF DAY and FBM STATUS

Time of day	FBM present	FBM absent	Total
8pm - 8am	9	4	13
8am - 8pm	7	4	11
Total	16	8	24

p - not significant

TABLE 21

MATERNAL PLASMA GLUCOSE CONCENTRATION and FBM

FBM present	FBM absent
n = 16	n = 8
4,7 ± 1,3 mmol/l	4,5 ± 0,5 mmol/l

experienced increasing abdominal pain. No placental pathology was found at caesarian section. The patient where no FBM was seen yet pregnancy continued, delivered spontaneously 12 days later of a healthy infant at 35 weeks gestation. The baby was on the 30th centile for gestation, showed no evidence of FBM on repeated scans and had an uneventful neonatal course. In both Marsals 1978 data (3 cases) and the recent case report mentioned (Hill et al 1984) preterm delivery ensued in spite of FBM, in the presence of an APH. It is not clear, however, whether further bleeds occurred in these cases subsequent to the scans.

The value of ultrasound in evaluating the third trimester patient with vaginal bleeding in preterm labour lies in its ability to confirm or rule out placenta praevia. There is a recognised lack of sensitivity in the ability of ultrasound to diagnose retroplacental bleeding. If the bleeding can drain vaginally from either a retroplacental or marginal location then the scan will reveal no abnormality. Jaffe et al (1981), in evaluating sonography in abruptio placentae, reported a sensitivity of 50%. In the study group of patients 7 of 14 (50%) with abruptions had ultrasonically detectable retroplacental clots - an identical sensitivity. Recently there have been reports of ultrasonically detected intra-amniotic blood clot with abruptio placentae (Jaffe et al 1981, McGahan et al 1982, Hill et al 1984). This was not seen in any patient in this series.

FBM do not aid in the prediction of a further retroplacental bleed but, should this not occur, the presence or absence of FBM correlates strongly with labour outcome. Treatment with β-mimetics would not be contemplated in this situation due to the cardiovascular side-effects and maternal risks from recurrent

haemorrhage. Thus, although reassuring at the time of investigation, the FBM findings would not alter patient management. The value of ultrasound lies in its ability to detect placental pathology.

CHAPTER 2 - 4

MULTIPLE PREGNANCY

Women carrying multiple pregnancies are at high risk of preterm delivery. As recorded earlier, approximately 40% will deliver preterm and this group of patients contributes substantially to the Early Neonatal Death statistics (25% of ENND). The Early Neonatal Deaths recorded in chapter 1 were all in infants weighing less than 1000gm and under 28 weeks gestation. This confirms the statement made by Claireaux (1970) that it is "the production of tiny, virtually non-viable infants that is mainly responsible for the high death rate in multiple pregnancy". These patients are also at greater risk of other pregnancy pathology including intrauterine growth retardation, premature spontaneous rupture of the membranes and antepartum haemorrhage from abruptio placentae. All these associated pathologies will alter obstetric management of preterm labour.

Patients and Methods

Eleven patients with "uncomplicated" twin pregnancies were admitted to the study. All had intact membranes and none had experienced vaginal bleeding. No fetus was growth retarded by either ultrasound measurement or paediatric assessment at delivery. One patient had a normal fetus and a fetus papyraceous found on scan and has been included in the multiple pregnancy group. No patient exhibited any signs of infection on admission. Both fetuses were scanned independently for the presence or absence of FBM as defined earlier.

Results

The FBM status of the fetuses in these twin pregnancies is seen in table 22. In these 11 cases FBM was present in both

TABLE 22

FBM and MULTIPLE PREGNANCY OUTCOME

Outcome	FBM present	FBM absent	Total
Continued > 1 week	4	1	5
Delivered < 1 week	4	2*	6
Total	8	3*	11

* In one of these pregnancies one fetus had FBM and the other did not

p - not significant

fetuses in 8 and in only 4 did pregnancy continue for greater than a week. In one of the remaining patients neither fetus showed FBM. Following intravenous Ritodrine the contractions ceased and pregnancy continued. Subsequent scans showed both fetuses to have FBM. In 1 of the 2 others there were FBM present in twin one but absent in twin two. This patient went on to deliver within 48 hours of scan. In the remaining patient there were no FBM in the leading twin and the second fetus was the fetus papyraceous mentioned above. This patient also delivered within 48 hours of the scan.

Discussion

It is evident from table 22 that FBM is of no value in predicting the outcome of preterm labour in multiple pregnancy. Little is known regarding FBM in multiple pregnancy and the relative incidence of FBM in the two fetuses. Marsal et al (1978) using A-scan, documented a decreased FBM incidence in the leading twin when the presentation was cephalic, implying some difference in relative incidence. This, however has not been confirmed or quantified.

The external influences that may effect FBM have been examined and, from tables 23 and 24, time of day and maternal plasma glucose concentration do not appear to effect the FBM findings. Only two patients were smokers and neither had smoked a cigarette within three hours of admission. In one of these smokers both fetuses had FBM, and in the other both were apnoeic. Both patients went on to deliver within 24 hours. No patient had imbibed alcohol prior to admission and none were on medication.

There is a similarity between these findings and those of uncomplicated singleton pregnancies with hydramnios. In both,

TABLE 23

FBM and TIME OF DAY

TIME OF DAY	FBM present	FBM absent	Total
8pm - 8am	4	1	5
8am - 8pm	4	2	6
Total	8	3	11

p - not significant

TABLE 24

MATERNAL PLASMA GLUCOSE CONCENTRATION and FBM

FBM present	FBM absent
n = 8	n = 3
4,6 ± 0,5mmol/l	5,13 ± 2,16mmol/l

the FBM status does not aid in the diagnosis of ongoing preterm labour and both are associated with excess uterine volume. It is possible that this increased uterine volume may trigger labour without effecting FBM by an, as yet, unknown mechanism. Turnbull et al (1983) commented that the mechanical effect of uterine overdistention is an important aetiological factor in preterm labour. This may be due to multiple pregnancy, hydramnios or both, and they documented an incidence of hydramnios as high as 10% in twin pregnancy. The authors postulated that the mechanism of labour may be abnormal changes in steroid hormone or prostaglandin production. None of the patients in this series exhibited hydramnios.

Clearly, in multiple pregnancy, FBM is of no value in the prediction of labour outcome.

CHAPTER 2 - 5

GENERAL DISCUSSION

Fetal Breathing Movement and Labour Outcome

From the preceding chapters it may be concluded that the clinical significance of FBM in relation to preterm labour outcome applies only to uncomplicated singleton pregnancies with intact membranes. The relationship between FBM and continuing pregnancy is lost when rupture of the membranes has occurred and in multiple pregnancy. In the antepartum haemorrhage group the relationship reaches statistical significance but tocolytic therapy is unlikely to be contemplated due to maternal dangers.

Thus, it is those patients that may benefit most from tocolytic therapy that are identified by this simple test. The test is not, however, 100% accurate and, although considerably better than our clinical criteria, does lead to false predictions as documented earlier.

Fetal Breathing Movement and Fetal Well-being in Preterm Labour

Several authors have investigated the relationship between antenatal FBM incidence and the clinical course of pregnancy. Marsal (1978) could find no correlation between FBM incidence and the subsequent course of pregnancy. Platt et al (1978) found a significant relationship between FBM and the outcome of pregnancy as judged by Apgar score and birth weight. Manning et al (1979) found a significantly higher proportion of reactive non-stress tests of fetal heart rate when FBM was present. Calvert and Richards (1979) considered the recording of a low FBM incidence to be predictive of fetal distress in labour. The development of the "fetal biophysical profile" by Manning, Platt and Sipos (1980), incorporating FBM amongst five biophysical variables, for

TABLE 25

FETAL BREATHING RELATED TO ADVERSE FETAL OUTCOME

	GESTATION	PREGNANCY PATH.	FBM	OUTCOME
Group A				
1.	28 weeks	Hydramnios	present	NND (NEC)
2.	27+weeks	Chorioamnionitis	present	BPD
3.	27+weeks	Chorioamnionitis	absent	SB
4.	29+weeks	Chorioamnionitis	absent	CP
Group B				
5.	28 weeks	Chorioamnionitis	absent	CP
6.	27+weeks	Chorioamnionitis	absent	BPD
7.	31+weeks	Chorioamnionitis	present	NND (Sept.)
8.	27+weeks	Chorioamnionitis	present	NND (Sept.)
9.	25+weeks	Chorioamnionitis	present	NND (Sept.+ extreme prem)
Group C				
10.	26 weeks	Abruptio Placenta	absent	NND (HMD + extreme prem)
Group D				
11.	27 weeks	nil	present	NND (HMD + prem + NEC)

NND - neonatal death ; NEC - necrotising enterocolitis

BPD - bronchopulmonary dysplasia; HMD - hyaline membrane disease

CP - cerebral palsy ; Sept. - septicaemia

the antenatal assessment of fetal well-being has been successful. Using this system Manning et al (1981a) have assessed 1184 high - risk patients and found it accurate in predicting fetal outcome.

The relationship between intrapartum FBM and fetal outcome has been addressed in the introduction. Wittman et al (1979) documented a significant association between absent or reduced FBM and an abnormal fetal heart pattern. No correlation was found between FBM and fetal outcome as judged by Apgar score at one and five minutes or the pH of the umbilical arterial blood. Richardson et al (1979) and Boylan and Lewis (1980) in their studies on FBM in labour at term concluded that fetal apnoea is normal during labour and has no adverse prognostic significance.

To assess whether the presence or absence (by defined criteria) of FBM found on admission in women in preterm labour leading to delivery has any prognostic significance for fetal outcome, adverse outcomes were examined. Eleven neonates in the study had poor outcome (defined as neonatal death or significant morbidity). The details of these babies are documented in table 25 along with FBM status on admission. Of these 11 patients, 9 delivered within 24 hours of admission and the remaining 2 within 48 hours of admission.

From the table, FBM was seen in 6 of the 11 fetuses on admission. If causes other than extreme prematurity and its sequelae are examined ie. numbers 1 to 8 only, then FBM was seen in 4 and absent in 4. The presence of FBM on admission does not exclude serious infection or other hazards for the preterm neonate at delivery. In contrast to the situation found antenatally, where presence of FBM is a good sign of fetal health, this reassuring aspect of FBM seems absent in preterm labour.

This is in agreement with the results obtained by Wittman et al (1979) in term fetuses in labour when no correlation could be found.

From table 25, undiagnosed infection is the major hazard.

The Role of Infection in Preterm labour

The discussion concerning the relationship between infection and preterm labour and which is cause and effect has continued unresolved for well over a decade. Infection in preterm labour has recently excited further interest. Its importance in prematurity is supported by the strong correlation between chorioamnionitis and preterm birth (Gravett 1984), and the association of various vaginal organisms with premature rupture of the membranes and preterm delivery (Minkoff 1983). The rate of sepsis in preterm infants is much higher than for those at term. This has been documented as 54 per 1000 for the former (Beauton et al 1965) and between 1 and 5 per 1000 for the latter (Klein and March 1976).

A causative relationship between infection and premature rupture of the membranes is circumstantial. Turnbull et al (1983) concluded that bacterial colonization and inflamation of the placenta was a consequence rather than a cause of premature rupture of the membranes (PROM). Minkoff (1983), however, considered that there was strong evidence to incriminate infection as the causative agent. Cederquist et al (1979), measuring cord immunoglobulin levels in infants whose mothers had PROM, found one peak of infection prior to 12 hours and a second peak after 72 hours post membrane rupture thus suggesting both cause and effect. Naeye and Peters (1980) found that amniotic

fluid infections appeared to be cause and not consequence of PROM since infections were two-to-threefold more common when the membranes ruptured just prior to labour, rather than just after its onset.

Concrete proof of infection as the cause of PROM and preterm labour, however, in the form of positive culture of organisms from vagina, placenta and neonate has been difficult to obtain (Zaaijman et al 1982). From the clinicians viewpoint few would consider tocolysis in the presence of ruptured membranes in the long-term and expectant management with PROM is encouraged (Daikoku et al 1981, Turnbull et al 1983).

Of more concern is silent chorioamnionitis in the presence of intact membranes causing preterm labour. These patients may be treated with tocolytics to their possible disadvantage. Ascending infection by bacteria through the cervix and across the intact membranes causing chorioamnionitis and congenital pneumonia is a well recognised phenomenon (Naeye and Peters 1978, Gravett 1984). Studies on amniotic fluid obtained by amniocentesis from women in preterm labour with intact membranes have been done. In three (Miller et al 1980, Bobitt et al 1981, Wahbeh et al 1984) the women were thought to be at risk of intrauterine infection on clinical criteria. Microorganisms were cultured from amniotic fluid in between 21% and 48% of these patients.

The true incidence of microbial invasion of amniotic fluid in preterm labour may have been overestimated due to the selection of these patients. This question has been addressed by Gravett et al (1983) and Hameed et al (1984) who have studied 91 women in total, in preterm labour with intact membranes,

singleton gestations and no clinical evidence of infection. Positive culture was obtained from 24% of amniotic fluid taken by transabdominal amniocentesis. These included bacteria (both anaerobic and facultative), yeasts (Candida albicans) and Mycoplasmas. In 4 of the above 5 studies anaerobic bacteria were the majority isolated indicating their importance. Mycoplasmas, particularly Ureaplasma urealyticum, appeared less pathogenic and pregnancies where this organism was isolated were no more at risk of preterm delivery than those with sterile amniotic fluid. Both Bobitt et al (1981) and Gravett et al (1983) found that patients whose amniotic fluid was colonised by bacteria or fungi were resistant to tocolytic therapy, and suggested that these organisms have a primary role in the aetiology of preterm labour.

A wide spectrum of organisms is implicated in preterm labour with little consistency in their isolation (Minkoff 1983, Gravett 1984). The anaerobe Fusobacterium was most prevalent. The picture becomes more confused when the association between pathogenic bacteria and the normal cervico-vaginal flora is investigated. Bejar et al (1981) documented Phospholipase A2 activty of microorganisms indigenous to the genital tract and within this group are all the organisms designated pathogenic from amniocentesis.

During pregnancy the number of bacterial species in the vagina declines with advancing gestation resulting in a more homogeneous flora than in the nonpregnant state (Goplerud et al 1976). Facultative bacteria remain largely unchanged but the prevalence of anaerobes decreases dramatically. Thus positive culture from high vaginal/cervical swabs may be suggestive of infection in the upper vagina or cervix but may bear no

relationship to what is going on in the uterus.

There is conflicting data regarding the significance of polymorphonuclear leucocytes in amniotic fluid. Miller et al (1980), Larsen et al (1976) and Hameed et al (1984) all demonstrated that their presence was indicative of infection. Listwa et al (1976) however, in a study of 95 patients, found no correlation between the presence of neutrophils and intrauterine infection.

The positive diagnosis of infection without culture of an offending organism is difficult and circumstantial evidence gives an easy but possibly inaccurate diagnosis. With this in mind a diagnosis of infection as the cause of preterm labour, with or without intact membranes, in the study was made only when two of the following three criteria were met.

(1) Subsequent evidence of maternal infection ie: pyrexia, tachycardia, offensive vaginal loss and/or positive pure culture of a pathogen from a high vaginal or cervical swab.

(2) Histological evidence of infection in the placenta and cord diagnosed by leucocyte infiltration of the membranes with or without microscopic observation of bacterial colonies in the tissues, or positive placental cultures.

(3) A positive neonatal infection screen within 24 hours of birth.

This was a retrospective diagnosis as no patient had evidence of infection on admission.

Of the 123 patients studied 27 (22%) were infected.

6 of 60 with contractions only (group A)

19 of 28 with PROM (group B)

1 of 24 with antepartum haemorrhage (group C)

TABLE 26

GESTATION	ORGANISM ISOLATED	OUTCOME
GROUP A		
27+weeks	Bacteroides Corrodene	Intrapartum SB
27+weeks	Nil - pus +++	Pneumonia and BPD
29+weeks	Anaerobic Streptococcus	CP
GROUP B		
28 weeks	Coliforms	CP
27+weeks	Group B Streptococcus	Pneumonia and BPD
31+weeks	Peptostreptococcus *	NND (Septicaemia)
27+weeks	Escherichia Coli *	NND (Septicaemia)
25+weeks	Streptococcus Faecalis	NND (Septicaemia)

* From the neonate within 24 hours of birth

SB - Still Birth

BPD - Bronchopulmonory Dysplasia

CP - Cerebral Palsy

NND - Neonatal Death

TABLE 27

ORGANISMS OBTAINED ON PURE CULTURE

Streptococci - Anaerobic = 8

Beta-haemolytic = 2

Coliforms = 3

Escherichia coli = 1

Haemophilus influenza = 2

Bacteroides species = 2

Neisseria gonorrhoea = 1

Gardnerella = 1

Staphylococcus epidermis = 1

1 of 11 with multiple pregnancy (group D).

There were 11 neonates in the study that experienced a poor outcome - defined as perinatal death or significant morbidity. Sepsis played a role in 8 of these patients. The details of these patients appear in table 26.

The cultures were obtained from swabs taken from the cervix on admission and the placenta and/or neonate at birth. It is important, in the light of recent publications (Gravett 1984) to note that routine cultures for the Mycoplasmas, specifically Ureaplasma urealyticum and Chlamydia trachomatis were not performed. In 21 of the 27 patients diagnosed as infected, positive cultures were obtained. The organisms cultured are listed in table 27.

As may be seen from both the group with poor outcome and those with no subsequent sequelae, there is a wide range of organisms that may act as pathogens. This is similar to the findings of many other investigators (eg. Zaaijman et al 1982, Minkoff 1983). The association between either cervico-vaginal colonisation with various organisms or positive cultures post delivery, and preterm labour does not prove causality. However, the existing evidence supports the hypothesis that genital tract infection and/or chorioamnionitis represents an important cause of preterm labour, (with or without PROM) and poor pregnancy outcome.

The mechanisms whereby infection may cause preterm labour are not fully understood but there are several possibilities. Infection of the maternal cervix may produce a direct toxic effect on the membranes. In vitro studies have shown that Chlamydia trachomatis can proliferate readily within human

amniotic cells (Harrison and Riggin 1979). Both in vivo studies in sheep and other in vitro studies using human membranes have demonstrated the ability of group B Streptococci, Escherichia coli, Bacteroides fragilis and Streptococcus intermedius to colonise within chorioamniotic membrane (Evaldson et al 1983, Galask et al 1984). Structural abnormalities within the membranes resulting from microbial invasion may contribute to premature rupture of the membranes and preterm labour.

Prostaglandins of the E and F group are powerful oxytocics and may initiate labour. It is by production of these substances that preterm labour may be initiated by infection. Formation of a purulent exudate in response to cervical or membrane infection brings together large numbers of leucocytes. These contain lysosomal Phospholipase A2 which releases free Arachidonic acid from the membrane phospholipids, from which prostaglandins are synthesised. The leucocytes themselves are capable of initiating prostaglandin (PG) synthesis as an integral part of the inflammatory response. Certain bacteria produce Phospholipase A2 which leads to the events described above. The microorganisms which produce the largest amounts of this enzyme include the anaerobic bacteria (Bacteroides, Fusobacterium and Peptostreptococcus) and Gardnerella vaginalis (Bejar et al 1981). It is noteworthy that in the study 11 of 21 patients with positive culture exhibited one or other of the above anaerobes.

An alternative interpretation of the finding of organisms in the amniotic fluid in patients with intact membranes has been proposed by Minkoff (1983). He proposed that, with advancing dilatation of the cervix and greater exposure of the fetal membranes, it was more likely that microorganisms would enter the

uterine cavity. This is supported by the findings at caesarian section where a higher incidence of organisms was found in advanced labour (Cooperman et al 1980). In the study by Bobitt et al (1981) there were only 16% infected when cervical dilatation was 3cm or less, whereas 42,5% with cervical dilatation of more than 3cm were infected - the numbers, however, are too small to draw any conclusions. In the present study 4 of the 6 patients with intact membranes had cervices less than 3cm dilated and the remaining two were both 3cm dilated. Thus they all fall into Bobitts first category. The criteria for inclusion in the study would have excluded those patients in advanced labour and the figures are a product of the study criteria and in no way reflect the true overall incidence of infection in preterm labour with intact membranes. The study figure of 10% is, however, similar to Bobitts 16% and Hameeds 14%. The weight of evidence supports an aetiological role for infection in preterm labour rather than it being a result of the labour. There may, however, be large geographical and/or population differences in the incidence of infection.

The study and the literature reviewed lead to the conclusion that silent chorioamnionitis may be a significant cause of preterm labour. It has been associated with preterm labour refractory to tocolytics (Wahbeh et al 1984, Hameed et al 1984) and I confirm this observation. It is important to ascertain whether tocolysis, given to patients in preterm labour with silent chorioamnionitis, delays delivery sufficiently to jeapardise the fetus by retaining it in a hostile enviroment.

In the study 13 of the 27 infected patients received intravenous tocolysis (48%). These included all 6 in group A, 6

of 19 in group B and the single group D patient. Of the 13, 6 delivered after 24 hours on tocolysis and 7 within 24 hours. There was 1 NND and 1 SB in the group who delivered after 24 hours and 2 NND, 2 BPD and 2 CP in those delivered within 24 hours, thus not indicating delay as being a contributory factor. This is confirmed by examining the data of Hameed et al (1984) and Wahbeh et al (1984). The number of patients, however, is very small and careful consideration will be necessary before any conclusions are drawn. Certainly, in the presence of infection, delivery occurs despite any efforts to prevent it.

The implications for the future assessment and management of uncomplicated preterm labour are considerable. It is of prime importance that a rapid, accurate and reliable method of detecting early infection in preterm labour be developed. The classical clinical signs of Gibbs et al (1980) represent late findings of amniotic fluid infection. Bacterial invasion of the liquor occurs several hours before the appearance of the classical signs of infection (Bobitt and Ledger 1978, Garite et al 1979), including maternal leucocytosis. The results of amniotic fluid leucocyte counts and Gram staining (Bobitt and Ledger 1978, Garite et al 1979, Larsen et al 1976, Listwa et al 1976, Miller et al 1980) and the quantitative culture of liquor (Bobitt and Ledger 1978, Miller et al 1980) are often non-specific or not immediately available.

Recently the assay of maternal serum for C - reactive protein has excited interest. C - reactive protein is a globulin that forms a precipitate when combined with the C - fraction of Streptococcus pneumonia. It is an acute phase protein present in patients with inflammatory lesions, bacterial infections and

tissue injury or necrosis. The assay is rapid using the C-reactive protein latex reagent (Calbiochem - Behring Rapi - tex C - reactive protein test), taking 20 minutes for a result.

Philip et al (1980) used the latex preparation successfully in predicting infection in the newborn. Evans et al (1980) used the C - reactive protein to help predict infection in patients with premature rupture of the membranes. Hawrylyshyn et al (1983) found C - reactive more reliable in detecting early infection with premature membrane rupture than maternal leucocyte counts and erythrocyte sedimentation rates. These investigators also noted that the C - reactive protein levels correlated better with pathologic confirmation of chorioamnionitis than with clinical morbidity. They advocated that this be used as a screening test for infection. The advantages of the test are that it is rapid, non-invasive, repeatable and cheap.

Hawrylyshyn et al (1983) found that urinary tract infection (present in 40% of the study population) was not a compounding factor in the interpretation of C - reactive protein. As this protein is non-specific and present with other infections this will need to be verified. It seems likely that the non-specificity of the test will lend itself to false positive results and it will thus need a more specific back-up.

An exciting finding by Gravett et al (1982) may provide this specificity in diagnosis. These investigators have found that organic acid metabolites from pathogenic bacteria are detectable in the liquor by gas - liquid chromatography (GLC). These results are preliminary but do address the problem at source and, if confirmed, may provide the means for very early diagnosis of bacterial invasion. A positive C - reactive protein may then be

followed by GLC of liquor from amniocentesis for these metabolites.

If our clinical ability to diagnose early infection improves then the use of FBM for targeting those women going on to preterm delivery and thus likely to benefit from tocolytic therapy will be invaluable. It will enable the clinician to rationally treat these patients and accurately assess current and future tocolytic efficacy.

CHAPTER 3

FETAL MOVEMENTS

The disappearance of subjectively perceived fetal movements in the second half of pregnancy is generally considered suggestive of fetal death. In many cases the mothers report that the cessation of fetal movements (FM) was preceded for several days by a change in the number and intensity of the movements. The relationship between fetal health and FM has stimulated many clinicians to use the subjective counting of FM by the mother as a clinical test.

Mathews (1973) suggested that FM counts may be useful in evaluating fetal well-being in growth retarded fetuses and Sadovsky and Yaffe (1973) introduced the concept of daily FM counts. Pearson and Weaver (1976) assessed daily FM counts in normal and high-risk pregnancies and found that a normal FM count was associated with good outcome whereas decreased FM preceded poor outcome. The predictive value of decreased fetal activity was, however, much less predictive of fetal compromise than normal FM was of a healthy fetus.

For more detailed information on fetal activity, objective methods for recording and quantifying FM have been devised. As detailed in the introduction, real-time ultrasound is well suited for this. Interpretation of the results is difficult owing to the complexity of fetal behavioral physiology and the number of external factors influencing FM.

As outlined earlier, FM has been studied during labour with real-time ultrasound (Wittman et al 1979, Richardson et al 1979, Boylan and Lewis 1980). Fetal movement was retained but decreased with progressing labour. Wittman et al correlated lack of fetal activity with an abnormal fetal heart trace in the labour.

The usefulness of this biophysical parameter in the prediction of labour outcome and assessment of fetal well-being in preterm labour was assessed.

Patients and Methods

The 123 women admitted with the diagnosis of early preterm labour and who underwent ultrasonic assesment for FBM in the previous chapter were studied.

Concommitant with the assement of FBM, FM were observed. A longitudinal view of the fetal trunk was obtained to record FBM and fetal trunk movements with event markers as described earlier. All movements of the trunk, excluding FBM and hiccups were recorded. Isolated limb movements with no movement of the fetal trunk were not recorded although it is my impression that most significant limb movements were associated with fetal trunk movement. Patients were scanned for a mean time of 30 minutes (range 16 - 60 minutes) and the results recorded as a percentage of the time scanned.

Results

The patients were divided into the same four groups as for FBM :-

A - Contractions only.

B - Spontaneous rupture of the membranes and contractions.

C - Antepartum haemorrhage and contractions.

D - Multiple pregnancy.

Table 28 details the percentage time of FM in the four groups. As can be seen, there is no significant change in fetal movements in relation to preterm labour outcome. Specifically in those women with contractions only this is in contrast to the situation with FBM which reduces dramatically in ongoing labour.

TABLE 28

RELATIONSHIP BETWEEN FETAL MOVEMENT AND PRETERM LABOUR OUTCOME

		DELIVERED	PREGNANCY CONTINUED	
Contractions only		15,5 ± 9,1	14,2 ± 7,4	N/S
n = 60				
SROM+Contractions		10,5 ± 8,9	11,8 ± 11,1	N/S
n = 28				
APH+Contractions		10,1 ± 6,1	11,25 ± 7,2	N/S
n = 24				
Twins	Δ1	11,0 ± 6,0	11,4 ± 8,8	N/S
n = 11	Δ2	12,2 ± 6,6	14,4 ± 5,0	N/S
Total		11,9 ± 8,4	12,6 ± 7,5	N/S

TABLE 29

FETAL MOVEMENTS and FETAL OUTCOME

Gestation	Pregnancy Pathology	FM(%)	Outcome
Group A			
1. 28 weeks	Hydramnios	25%	NND (NEC)
2. 27+weeks	Chorioamnionitis	2%	SB
3. 27+weeks	Chorioamnionitis	7%	BPD
4. 29+weeks	Chorioamnionitis	2,7%	CP
Group B			
5. 28 weeks	Chorioamnionitis	1%	CP
6. 27+weeks	Chorioamnionitis	0%	BPD
7. 31+weeks	Chorioamnionitis	2%	NND (Sept)
8. 27+weeks	Chorioamnionitis	2,2%	NND (Sept)
9. 25+weeks	Chorioamnionitis	0,6%	NND (Sept + prem.
Group C			
10. 26 weeks	Abruptio Placenta	2%	NND (HMD +asphyxia)
Group D			
11. 27 weeks	Nil	16%	NND (HMD + NEC)

NND - Neonatal death,

CP - Cerebral Palsy,

BPD - Broncho-pulmonary dysplasia,

SB - Still-birth,

HMD - Hyaline membrane disease,

NEC - Necrotising enterocolitis.

In view of its usefulness in antenatal surveillance for fetal compromise this aspect has been addressed.

Relationship between FM and fetal outcome

In chapter 2 the role of infection was highlighted. Of the 123 women in the study 27 had chorioamnionitis. The mean duration of FM in this group was 10,0 ± 9,5 (range 0 - 38%) which was not significantly different from the non-infected group (12,1%). Thus this parameter, as with FBM, gives no early indication of infection.

Poor outcome - defined as perinatal mortality or significant morbidity - occurred in 11 patients as detailed earlier. Table 29 gives details of these patients along with the incidence of fetal movement recorded for each. If causes other than prematurity are examined these include patients 1 to 8. In these fetuses FM occurred 5,2% of the time, a significant reduction in FM ($p<0,01$).

If a cut-off of 3% FM is made then 17 of the 123 patients in the study are included. Three were normal pregnancies and 14 had intrauterine pathology (13 infection and 1 retroplacental clot). Six of the 8 with poor outcome fall into this group. Infection causing fetal compromise (possibly septicaemia in utero) is evidenced by a decrease in FM whereas chorioamnionitis without fetal involvment does not significantly affect fetal activity.

Discussion

Biophysical parameters are well established and used successfully for fetal surveillance in the antenatal period. (Manning et al 1980b, Sadovsky 1981). Their use in labour, both term and preterm, has received little attention. As documented earlier Wittman et al (1979) correlated lack of FM and FBM with

pathological fetal heart traces in labour. No correlation was found with fetal outcome as judged by Apgar scores or the pH of umbilical arterial blood. These patients were in active spontaneous or induced labour. No percentage quantitation of FM to time scanned was recorded. The authors noted a significant correlation between FM and contractions and concluded that contractions may stimulate the fetus to move.

Boylan and Lewis (1980) demonstrated no significant reduction in FM in labours with normal outcome. However, these patients ranged from early labour (cervix 2cm dilated) to advanced labour at 9cm dilatation. No distinction was made between those in early and advanced labour. In contrast Richardson et al (1979), in their longitudinal study of patients electively induced at term, showed a significant reduction in FM from a control period to active labour. However, gross FM during the latent phase of labour did not differ significantly from that observed during the control period or active phase of labour indicating a progressive decrease rather than a sudden one. Thus, both Wittman et al and Richardson et al have demonstrated a reduction in FM during active labour. It is possible that in Boylan and Lewis' study this was not apparent as more patients were in the latent rather than active phase of labour. Thus, means of single observations in the control period and during labour did not change significantly.

From the results no change in FM occurs with the onset of preterm labour and as a predictor of labour outcome this parameter is of no value. Infection, unless it is causing fetal compromise, cannot be detected by FM incidence. A reduction in FM identifies the majority of fetuses destined to experience a

poor outcome.

In those fetuses exhibiting less than 3% FM only 3 of the 17 pregnancies were normal. Six of the 8 fetuses who subsequently had a poor outcome from causes related to their intrauterine environment recorded FM of less than 3%. The mean period of scanning for this group was 45 minutes.

In spite of the wide inter - and - intra fetal variation in FM a significant reduction to less than 3% of time scanned reliably identified those fetuses at risk, particularly with reference to fetal infection. Biophysical parameters, however, vary considerably in incidence depending on the length of time for which they are observed. It would thus seem appropriate that a period of at least 30 minutes should elapse before decreased FM is suspected.

Preterm labour is no different to labour at term with respect to FM. In the normal healthy fetus FM does not decrease significantly during the latent phase of labour. In fetuses with intrauterine pathology affecting the fetus a reduction in FM occurs. The curious aspect of this phenomenon is that all these fetuses, prior to being entered into the study, exhibited normal healthy fetal heart traces. This reduction in FM may nevertheless be related to fetal compromise similar to the findings in the antenatal period (Manning et al 1981a).

Ten of 17 fetuses with less than 3% FM had normal outcomes (58%) and 7 (42%) did not (although intrauterine pathology was present in 14 of the 17). Six of 8 (75%) of the fetuses with poor outcome were identified and 6 of 7 compromised by infection were in this group. The predictive value of a negative result (ie; a finding of normal activity) was high but the predictive

value of decreased activity was much less indicative of fetal compromise.

A significant reduction in gross FM in early preterm labour, even in the presence of a normal fetal heart trace and with no overt signs of infection, should alert the clinician that the fetus may be at risk.

CHAPTER 4

THE CERVIX

The use of ultrasound for assessing the state of the cervix in preterm labour has received little attention. A few case reports (Sarti et al 1979, Redford et al 1981) describe visualisation of the cervix and bulging membranes in patients in advanced preterm labour. No systematic assessment of the accuracy or usefulness of ultrasonic cervical measurement in preterm labour had been performed at the time work for this thesis had begun. As outlined in the introduction, ultrasonic assessment of the cervix for cervical incompetence is technically feasible although of doubtful value.

Digital cervical assessment of patients in preterm labour plays a significant role in the diagnosis of ongoing preterm labour despite its unreliability. In this study I have sought to ascertain the accuracy of ultrasound measurement of the cervix and to assess its value in the prediction of preterm labour outcome.

PATIENTS AND METHODS

Cervical measurement was performed on the 123 patients admitted to the study. The method used for examining the cervix was as described by other authors (Mahran 1980, Bernstine et al 1981). The patient was required to have at least a partially full bladder in order to visualize the cervix. The ultrasound examination was not delayed in order to achieve this but, on admission, the patient was not asked to produce a urine sample until after the scan. This usually resulted in adequate bladder distention as visualization of the cervix was performed after assessment of fetal breathing movements and fetal movements for up to 60 minutes.

Using a linear array real-time scanner with 3,5MHz.

transducer an initial transverse scan was performed to delineate the lateral borders of the cervix. Thereafter a longitudinal view down the centre of the cervical canal was obtained and measurements of length and dilatation made. In all except two patients (those with placenta praevia) a vaginal examination was then performed to digitally measure the cervical dilatation and length. This digital measurement was performed by a senior member of the on-call staff who did not know the ultrasound findings.

RESULTS

Patients were divided into the four groups of their presenting pathology. viz;

A. Contractions only.

B. Antepartum haemorrhage and contractions.

C. Spontaneous rupture of the membranes and contractions.

D. Multiple pregnancy.

The results of the cervical measurements found in these four groups may be seen in table 30.

The two patients in whom errors in ultrasound measurement of the cervix occurred both had fully effaced cervices and erroneous measurments were obtained. These errors were both in the measurement of dilatation, one an overestimate and the other an underestimate. Of 123 patients studied, in only 12 (10%) was visualization not achieved. Thus, of the 111 patients scanned, correct measurements were obtained in 109 (98,2%). A bulge of membranes through the internal os was seen in 4 pastients and in one of these a loop of umbilical cord and a hand were seen presenting resulting in delivery by caesarian section. Bulging membranes were not a common feature in those patients who went on

TABLE 30

ULTRASONIC CERVICAL MEASUREMENT IN PRETERM LABOUR

	PREGNANCY CONTINUED		PATIENT DELIVERED		NOT SEEN
	Dil	Length	Dil	Length	
Contr.only	1,52	1,45	2,28	1,25	5(8,3%)
n = 60	±0,79	±0,6	±0,96	±1,1	
APH	1,2	1,8	1,88	1,2	1(4%)
n = 24	±0,4	±0,4	±1,1	±0,7	
SROM	1,5	2,0	1,5	1,65	5(17%)
n = 28			±0,8	±0,6	
Twins	2,5	1,0	1,9	1,3	1(9%)
n = 11	±0,8	±0,65	±1,0	±0,45	

to deliver within a week of scan.

In none of the groups did the differences in cervical measurements between those who delivered and those where pregnancy continued reach statistical significance. However, in all groups the trend was for those going on to deliver to have more widely dilated and shorter cervices.

A failure to observe the cervix in 12 (10%) of the women was due to the low station of the presenting part (3), inadequately filled bladder (4), or lack of liquor (5). In the two patients where incorrect measurements were made the cervix was too effaced to be easilly visualized and an error was made.

DISCUSSION

The ability to observe the cervix in preterm labour is a desirable facility as vaginal examination may be contraindicated. In the presence of ruptured membranes infection may be introduced thus dramatically altering the course of the pregnancy. Work published from Oxford (Mitchell et al 1977) demonstrated a rapid rise in Prostaglandin F2' following vaginal examination. This may stimulate further uterine activity thus increasing the risk of labour progressing.

This study demonstrates that it is possible, with standard equipment and very little delay, to visualise the cervix in the majority of women (90%) even in the presence of ruptured membranes (82%). The observations in this series were made with a linear array transducer which is not ideally suited for this purpose due to its large physical size. The smaller, more manouvreable sector scanner would, no doubt, enable measurement in a higher proportion of patients.

The mean length of the cervix in all groups was somewhat

shorter than those previously published (Vaalamo and Kivikoski 1978, Bernstine et al 1981, Zemlyn 1981) being between one and two centimeters. This may be due to :-

1. Gestational difference - the published data being in pregnancies of early gestation.

2. Less bladder filling and thus a decrease in the degree of cervical elongation that has been remarked on by the other authors.

These findings are confirmed by a recent study by Bartolucci et al (1984). The ultrasonic measurement of the cervix in preterm labour does not have any predictive power for labour outcome and mirrors the clinical findings of Anderson and Turnbull (1969). However, this study does indicate that cervical measurement by ultrasound is accurate, practically feasible and would obviate the need for a vaginal examination in the majority of women admitted in early preterm labour.

PART II

THE RELATIONSHIP BETWEEN PROSTAGLANDIN E AND THE CESSATION OF FETAL BREATHING MOVEMENT WITH THE ONSET OF LABOUR

CHAPTER 5: THE ABSORPTION PROFILE OF EXOGENOUSLY ADMINISTERED PROSTAGLANDIN E2.

CHAPTER 6: MATERNO - FETAL TRANSFER OF PROSTAGLANDIN E2 IN THE SECOND TRIMESTER.

CHAPTER 7: FETAL BREATHING MOVEMENT AT TERM AND EXOGENOUSLY ADMINISTERED PROSTAGLANDIN E2.

CHAPTER 5

THE ABSORPTION PROFILE OF EXOGENOUSLY ADMINISTERED PROSTAGLANDIN E2

From the introduction and the findings in the first part of this thesis, FBM is reduced with the onset of normal spontaneous or induced labour. The role played by Prostaglandin E in this reduction of FBM is examined in the second part of this thesis.

As outlined in the introduction, the concept that Prostaglandin E (PGE) is involved in this process has arisen from direct animal and circumstantial human neonatal data. However, lack of a reliable and accurate assay for PGE has hindered clarification of this phenomenon.

Reliable plasma radio-immunoassay of PGE2 has been hampered by both analytical and physiological factors. The primary prostaglandin is rapidly inactivated in vivo to its 15-keto-13,14-dihydro metabolite (PGEM) with one circulatory pass through the lungs (Ferreira and Vane 1967). Peripheral blood levels may, therefore, reflect pulmonary efficiency in metabolising PGE rather than its tissue synthesis and release. Artefactual PGE production may compound the difficulties and arises from incorrect handling and storage of blood samples (Smith et al 1973, Jubiz and Frailey 1974). To overcome these problems the develpoment of a prostaglandin metabolite assay has been attempted. This has proved successful for Prostaglandin F metabolite (Granstrom and Kindahl 1976) but because of the chemical instability of Prostaglandin E metabolite (PGEM) in blood (Fitzpatrick et al 1980, Granstrom et al 1980) development and validation has been difficult.

Depending on time, temperature, pH and albumin concentration PGEM breaks down to 13,14-dihydro-15-keto PGA2 (PGAM) which in turn can bind to albumin (Fitzpatrick et al 1980). All of these metabolite forms, however, can be quantitatively converted under

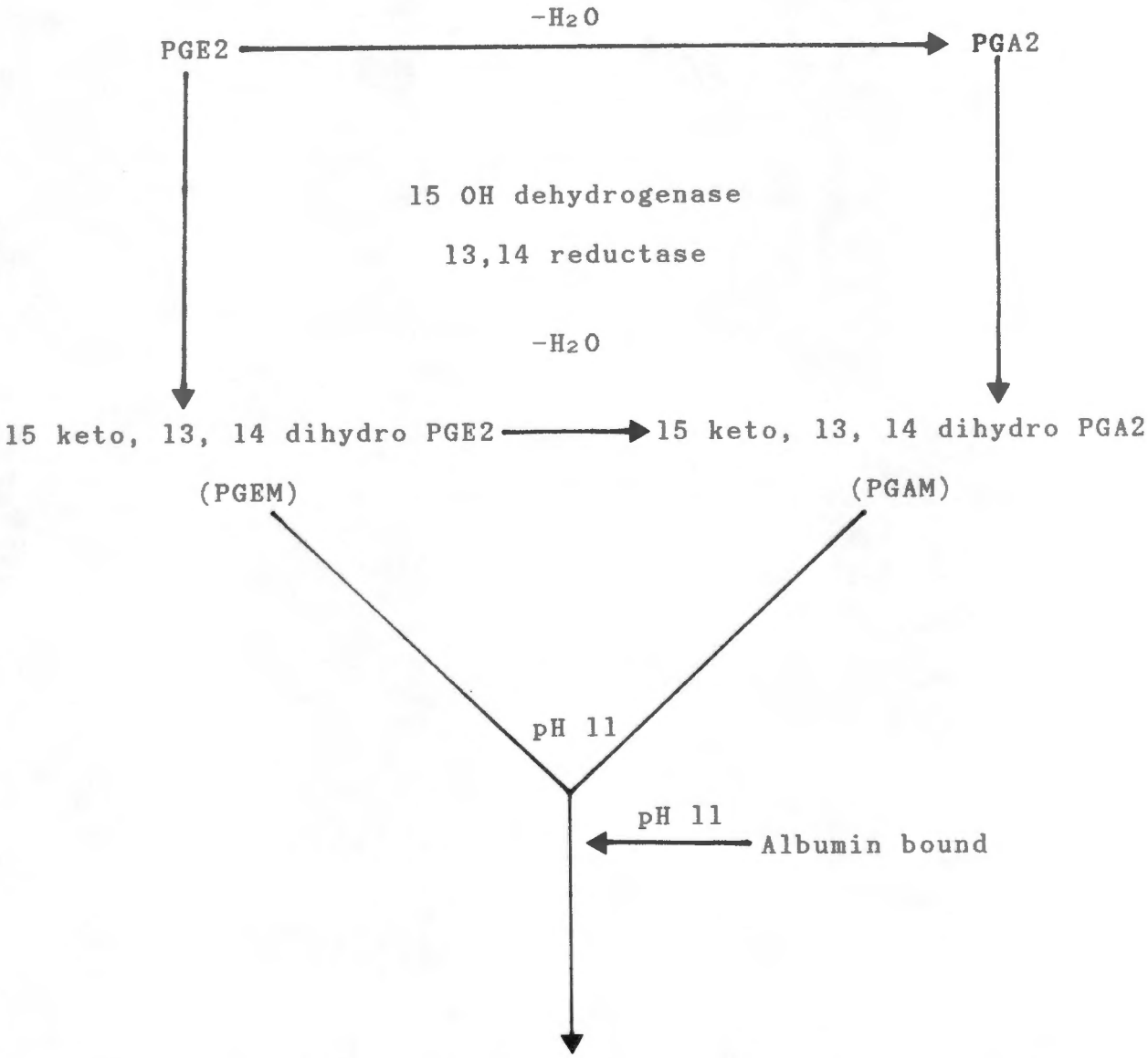


Fig 2 - The bicyclo-PGEM pathway

alkaline conditions (pH 11,0) to a stable bicyclo compound (fig2) 11-deoxy-13,14-dihydro-15-keto-11β,16ε-cyclo-PGE2 (bicyclo-PGEM) (Fitzpatrick et al 1980, Granstrom et al 1980). The development and validation of a radio-immunoassay (RIA) for the bicyclo-PGEM compound has recently been achieved (Bothwell et al 1982, Demers et al 1983). This now provides a simple and reliable direct RIA for bicyclo-PGEM which circumvents the problem of PGEM instability and permits reliable estimation of PGE2 metabolite levels in plasma. Using this assay I have sought to clarify the role played by PGE2 in the reduction of human FBM with labour.

Unlike animal studies where direct infusion of PGE2 into the fetus is possible causing fetal apnoea (Kitterman and Liggins 1980), direct human data is not available. Prostaglandin E2, however, is extensively used intravaginally to ripen the cervix prior to the induction of labour, and for induction itself (MacKenzie and Embrey 1977, Embrey 1981). It has been established that fetuses delivered following exogenously (intravaginal) administered PGE2 have significantly higher levels of PGE in the cord venous blood at delivery than those following spontaneous labour (MacKenzie et al 1980a). There was no evidence that the time interval between treatment and delivery, or the dosage of PGE2, influenced cord levels. This data seems to indicate that high levels of exogenously administered prostaglandin reaches the fetal circulation.

To further investigate this it has been necessary to establish the absorption profile of PGE2 administered vaginally. A number of different vehicles into which PGE2 has been incorporated have been used. These include :-

1. Glyceride based pessaries (Witepsol E75).

2. Methyl-hydroxy-ethyl cellulose gel (Tylose MH 300 : Hoechst UK. Ltd.)

3. Tablets containing 0,5 and 3mg PGE2 (Upjohn Ltd.)

The practice at the John Radcliffe Hospital in Oxford is to use the Witepsol pessaries for cervical ripening and labour induction and the absorption profile from this preparation has been studied.

PATIENTS AND METHODS

Ten patients scheduled for mid-trimester therapeutic abortion were recruited to the study. Informed consent was obtained and patients were randomly asigned to be treated with 10mg.PGE2 in a Witepsol pessary administered vaginally or to act as controls (5 patients in each group). Prior to any vaginal procedure being performed an intravenous cannula was inserted for venous blood sampling, and a 7ml. sample of blood taken.

All blood samples were free flowing venous blood taken into plastic centrifuge tubes containing Salicylic Acid (a Prostaglandin Synthetase inhibitor) and Ethylene-diamino-tetracetic acid (EDTA- an anticoagulant). These were kept on ice for up to 30 minutes until centrifugation at 1000G and 10 degrees centigrade for 15 minutes. Plasma was removed and stored at -20 degrees C until assayed for bicyclo-PGEM. The assay was performed as a single batch to ensure that no inter-assay variation occurred.

The treatment group then had the Witepsol pessary inserted into the posterior vaginal fornix. A 16 gauge Foley catheter was inserted through the cervix in both groups to measure intrauterine pressure changes. Blood samples were taken at 30 minutes and 60 minutes post treatment and hourly thereafter for 6

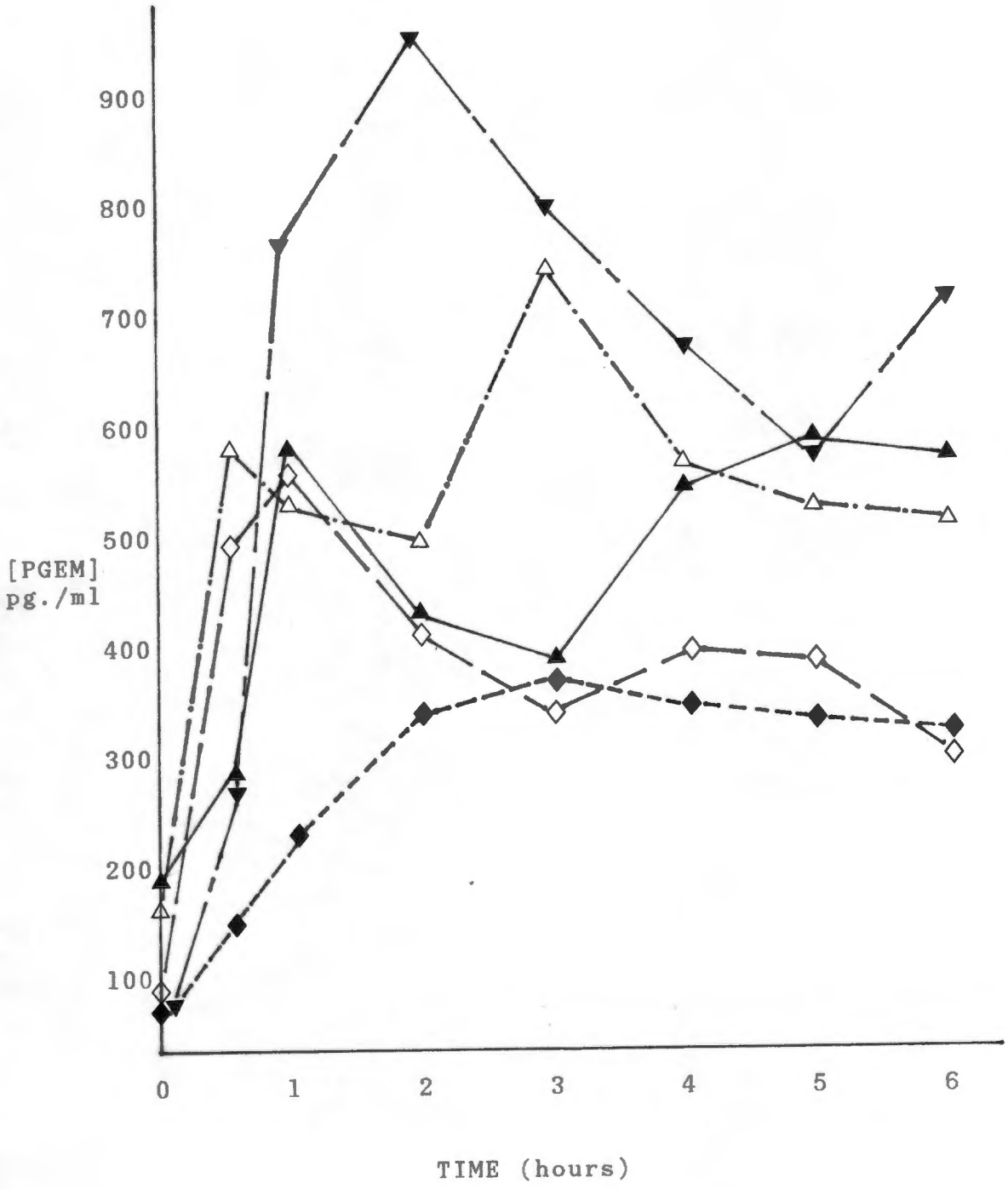


Fig 3 - Concentrations of bicyclo-PGEM in individual patients treated with 10mg. PGE2 in a Witepsol pessary.

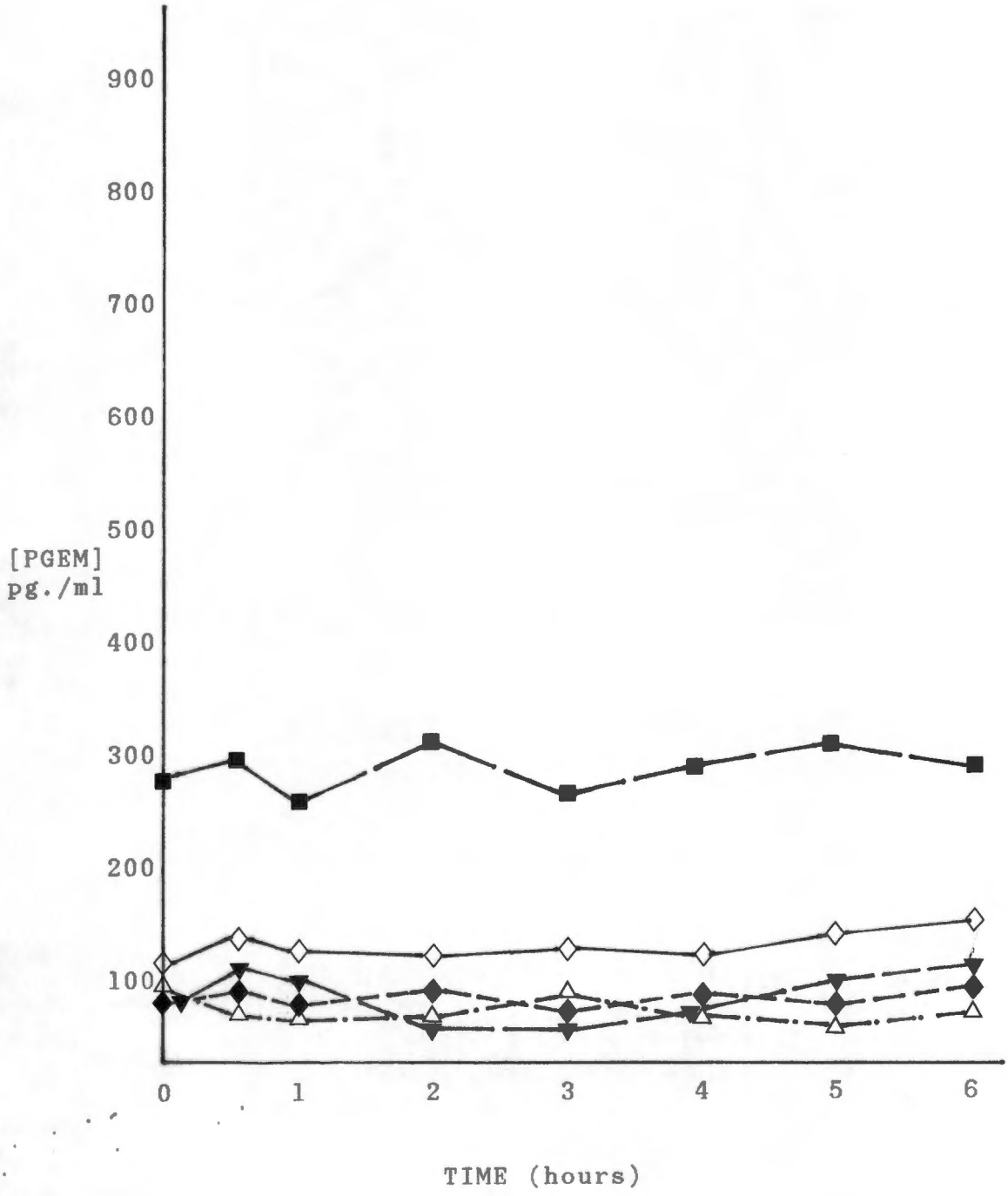


Fig 4 - Concentrations of bicyclo-PGEM in individual control patients

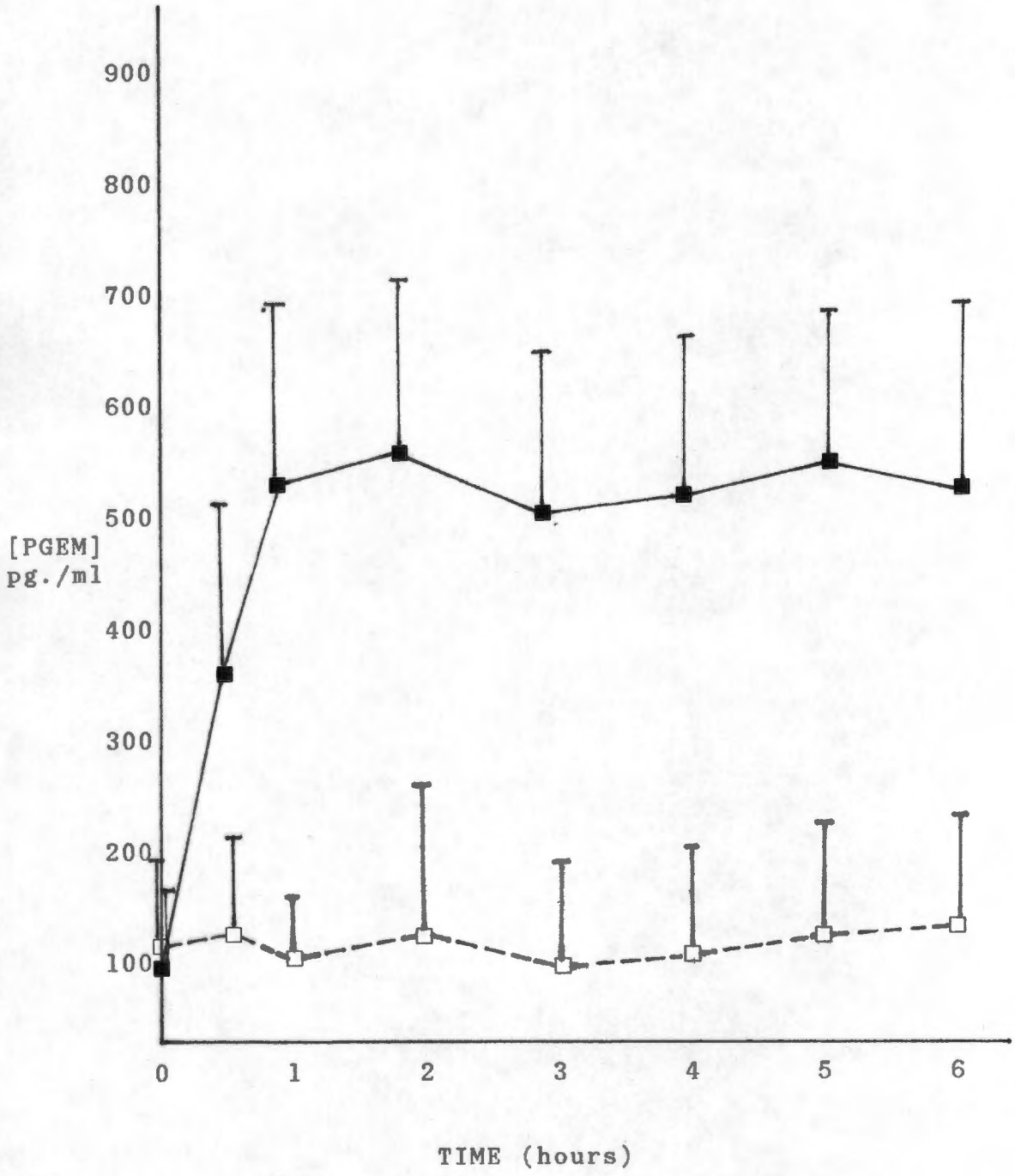


Fig 5 - Relative concentrations of bicyclo-PGEM in the treatment and control groups (meaned values with SD).

hours.

RESULTS

The levels of bicyclo-PGEM measured in the plasma of these patients are documented in figures 3 and 4. The relative meaned concentrations for the two groups may be seen in Fig. 5.

There was a very rapid rise in bicyclo-PGEM following administration of the Witepsol pessary in the treatment group (Fig.3). This rise plateaued off at 1 hour but remained at this high level (±500pg/ml) for the full 6 hours of sampling. Large variations in the peak levels are evident but the pattern remained very similar for each patient. No significant change in bicyclo-PGEM levels occurred in the control group.

DISCUSSION

All previous work done on the absorption patterns of PGE2 from vaginal preparations have used the 13,14-dihydro-15-keto PGE2 assay which has the inaccuracies documented earlier. Gordon-Wright and Elder (1979) studied absorption patterns from various preparations including Witepsol H15. Only three patients given the Witepsol pessary were studied and no pattern of absorption could be established. No other data is available for Glyceride based pessaries.

This data demonstrates that a rapid and sustained rise in bicyclo-PGEM occurs following vaginal administration of PGE2 in a Glyceride based pessary. Demers et al (1983) have demonstrated that bicyclo-PGEM is rapidly removed from the circulation. Thus, these sustained levels of bicyclo-PGEM indicate a sustained release of PGE2 into the maternal circulation for the duration of sampling.

With this absorption pattern elucidated it is now possible

to study the transfer of PGE2 to the fetus during maximal maternal circulating concentration.

CHAPTER 6

MATERNO - FETAL TRANSFER OF PROSTAGLANDIN E2 IN THE SECOND TRIMESTER

In chapter 5 the absorbtion pattern of exogenously (intravaginal) administered PGE2 has been established. In order to confirm MacKenzie et al's (1980a) findings of direct transfer of PGE2 to the fetus, direct fetal blood sampling following vaginally administered PGE2 was performed.

PATIENTS AND METHODS

Ten patients admitted for therapeutic termination of pregnancy for reasons other than fetal anomaly were studied. Their gestations ranged from 18 to 24 weeks. Due consideration was given to the recommendations of the Report of the Advisory Group for the use of fetuses in research (DHSS 1972) and ethical approval for fetoscopic research had previously been granted by the Ethics Committee of the local hospital. Full informed and signed consent was obtained from all patients. They were then randomised into a treatment or control group (5 patients in each).

Prior to any procedure being performed an intravenous cannula was inserted and a 7ml. blood sample taken for estimation of the maternal resting circulatory level of bicyclo-PGEM. All blood samples (maternal and fetal) were handled and stored as described in the previous chapter. Following sampling a 10mg Witepsol pessary was inserted into the posterior vaginal fornix of the treatment group. Fetoscopy and fetal blood sampling was performed 2,5 hours later. A repeat maternal sample was taken at this time. In the control group fetoscopy was performed at a convenient time.

One to two hours prior to operation, 20mg of Papaveretum was given intramuscularly as premedication in both groups. Five milligrams of Diazepam was given intravenously immediately before

fetoscopy. With the patients bladder empty, an ultrasound examination of the uterus was made with a General Electric "Dataline" real time scanner. This localized the placenta and determined the site of entry into the amniotic cavity avoiding fetus and placenta. Local anaesthesia was induced at the site of entry with 7 to 10ml of 1% Xylocaine in Epinephrine solution. This was injected into the abdominal wall with infiltration extending into the myometrium.

All examinations were performed with a Stortz fetoscope (26300 C) incorporating a side channel to accommodate a 22 gauge purpose designed needle (MacKenzie et al 1980b). A Hopkins minature "foreward - oblique 30 degree" telescope (27018 A) was used for visualisation. After insertion of the fetoscope, orientation within the amniotic cavity was made with identification of the placental site and fetal landmarks. Needle aspiration from both an artery and the vein was performed at a convenient point along the umbilical cord's length, ideally near its placental or fetal insertion.

The aspiration was accomplished under direct vision to ensure that the needle remained within the vessel lumen thus avoiding contamination with amniotic fluid. Two millilitres of blood was aspirated from each vessel and put into 10% by volume of Salycilic Acid and EDTA.

A further 0,5ml sample was aspirated from each vessel into heparin at the time of sampling to confirm the vessel of origin using previously determined (MacKenzie, Castle and Johnson 1985) normal blood gas values for umbilical artery and vein in the second trimester. Additional confirmation that the blood was of fetal origin was made using the acid elution technique of

TABLE 31

Maternal bicyclo-PGEM levels

Controls		Treatment Group		
		Pre-treatment		3 hours post treat.
238		122		341
126		109		342
172	p-not significant	110	p<0,01	309
217		256		553
261		262		731

TABLE 32

Fetal umbilical vein bicyclo-PGEM

Control Group	Treatment Group
97	123
102	132
104	143
110	152
161	342

$p < 0,01$

TABLE 33

Fetal umbilical artery bicyclo-PGEM

Control Group	Treatment Group
96	112
101	113
106	126
108	183
124	254

$p < 0,05$

Kleihauer et al (1957). After the sampling 5mg of PGE2 was inserted intra-amniotically to induce abortion.

RESULTS

Successful pure fetal blood sampling from both umbilical artery and vein was achieved in all 10 cases studied. There were no maternal complications as a result of the fetoscopies either immediately or subsequently. Results were analysed using the Wilcoxon Rank Sum test.

Tables 31, 32 and 33 detail the results of the bicyclo-PGEM assay on maternal, fetal umbilical vein and fetal umbilical artery plasma. As in the previous chapter all samples were assayed in a single assay batch to eliminate inter-assay variation.

There was no significant difference between the maternal control and pre-treatment samples. Following PGE2 administration a significant rise ($p<0,01$) in maternal circulating levels of bicyclo-PGEM occurred relative to both the controls and the pre-treatment values. This is as expected from the findings in chapter 5. Following maternal administration of PGE2 a significant rise in both fetal venous ($p<0,01$) and arterial ($p<0,05$) concentrations of bicyclo-PGEM occurred. No significant arterio-venous difference existed in either group in accord with recent observations near term (Brennecke et al 1985).

DISCUSSION

From this data it may be concluded that the rise in maternal circulating PGE2, and hence bicyclo-PGEM concentration, is mirrored by a rise in fetal circulating bicyclo-PGEM. This occurs in the non-labouring state, and appears to indicate that exogenously administered PGE2 enters the fetus as in labour

(MacKenzie et al 1980).

However, the assay used in these experiments is for the metabolites of PGE2 and not the active substance which, as documented earlier, is rapidly broken down. It is thus not possible to say whether the active prostaglandin is crossing to the fetus and being metabolised thereafter, or whether the metabolites of PGE2 measured by both MacKenzie et al (1980) and myself cross to the fetus in their inactivated form. In the unlikely event that an assay for active PGE2 in plasma becomes available and the instability problems can be overcome, this question may be answered.

Circumstantial evidence may give us a clue to this. Exogenously administered prostaglandin effectively stimulates uterine activity in both the mid-trimester (Karim and Amy 1975) and at term (Embrey 1975). It has been established that this substance is rapidly inactivated in the pulmonary circulation (Ferreira and Vane 1967). Thus it is reasonable to conclude that the active substance (PGE2) enters the local uterine circulation to exert its effect prior to entering the maternal venous system. This being so, transplacental transfer of PGE2 may well occur leading to raised fetal levels of the active substance and consequently bicyclo-PGEM.

Finally, these observations have been made in the second trimester patient. Differences may arise in both maternal absorption and fetal transfer at or near term. This question will be addressed in the following chapter.

CHAPTER 7

FETAL BREATHING MOVEMENT AT TERM AND EXOGENOUSLY ADMINISTERED PROSTAGLANDIN E2.

In the preceding two chapters attempts have been made to elucidate the absorption pattern of PGE2 from an exogenous vehicle and document fetal circulatory levels following this administration. This data has enabled me to ascertain when the maximal maternal circulating levels are reached and whether, at this time, increased fetal levels are apparent. The arbitrary time of two and a half hours post administration was chosen as, in chapter 5, it was shown that the circulating level maintained a plateau value at this time. To investigate the effect of exogenously administered PGE2 on human FBM, women at term scheduled for induction of labour following vaginal PGE2 administration were studied.

PATIENTS AND METHODS

Twenty five patients at 39 to 42 weeks gestation with completely uneventful singleton pregnancies were recruited. Fifteen patients were scheduled for induction of labour following PGE2 pre-treatment to the cervix. The remaining ten patients were due to have elective caesarian sections for cephalo-pelvic disproportion and acted as controls. All these women and their fetuses were entirely normal with no known pregnancy pathology.

Following informed consent, a 30 minute real-time ultrasound scan (using the machine and methods described in part I of this thesis) to quantify FBM was performed. FBM was recorded on an on-line computer (Rockwell AIM 65) using an event-marker interupt system. This was purpose built and programmed to record the total number of breathing movements, the breath-to-breath interval, the time spent breathing and the total apnoea (defined as a period greater than 5 seconds). After 30 minutes this information was printed out including a breath-to-breath interval histogram. A

maternal venous blood sample was taken for bicyclo-PGEM assay and into Sodium Fluoride for blood glucose measurement.

The control group then underwent their caesarian sections and a sample of umbilical cord venous blood was taken for the bicyclo-PGEM assay. In the treatment group, following FBM quantitation and maternal blood sampling, a Witepsol pessary containing PGE2 was inserted into the posterior vaginal fornix. Nulliparous women (n = 4) received 5mg PGE2 and the multiparae (n = 11) 2,5mg of PGE2.

Two and a half hours following administration a repeat scan for FBM quantitation was performed for a further 30 minutes. Thereafter maternal blood was again sampled for bicyclo-PGEM and blood glucose assays. At delivery the time interval between scan and delivery was noted and maternal and cord venous blood taken for bicyclo-PGEM assay. All samples were taken, handled and stored as described in chapter 5 and assayed as a single batch.

RESULTS

The patients may be divided into three groups.

1. The caesarian section (control) group ; n = 10.
2. The induction group where FBM continued ; n = 9.
3. The induction group where FBM ceased ; n = 6.

The results for FBM, bicyclo-PGEM assay and random blood sugar estimation are seen in tables 34, 35 and 36. In the caesarian section group FBM occurred for 43,4 ± 26,4% of the time. There was no difference between this value and the pre-treatment values in the induction groups (see table 34). In group 2 (where FBM continued), following PGE2 administration, FBM occurred 35,2 ± 24,7% of the time scanned which is not significantly different from the incidence prior to treatment.

TABLE 34

FBM AND MATERNAL PGE2 ADMINISTRATION

	CONTROL PERIOD	3 HOURS POST TREATMENT
GROUP 1	43,4 ± 26,4%	-
GROUP 2	40,8 ± 28,8%	35,2 ± 24,7%
GROUP 3	37,1 ± 14,5%	< 1%

TABLE 35

BICYCLO-PGEM LEVELS AND MATERNAL PGE2 ADMINISTRATION

	MATERNAL			FETAL
	CONTROL PERIOD	3 HOURS POST Rx	DELIVERY	CORD VEIN
GROUP 1	154 ± 35	-	154 ± 35	206 ± 99
GROUP 2	144 ± 17	754 ± 252	318 ± 123	834 ± 233
GROUP 3	164 ± 48	613 ± 189	405 ± 163	628 ± 252

all bicyclo-PGEM levels are in pg/ml

TABLE 36

RANDOM BLOOD SUGAR ESTIMATIONS

	CONTROL PERIOD	3 HOURS POST TREATMENT
GROUP 1	4,0 ± 0,4	-
GROUP 2	4,4 ± 0,3	4,5 ± 0,9
GROUP 3	4,6 ± 1,8	4,7 ± 1,1

In group 3 (where FBM ceased) the incidence of FBM decreased to less than 1%.

Maternal bicyclo-PGEM levels in the three groups during the control period showed no significant difference (table 35). Three hours after vaginal PGE2 administration bicyclo-PGEM levels in the induction groups (groups 2 and 3) had risen significantly ($p<0,001$). There was no significant difference in the post treatment levels in those women where FBM continued or where it ceased. The levels at delivery were still significantly higher than those prior to treatment ($p<0,01$) but had dropped significantly from the 3 hour level. Cord venous bicyclo-PGEM rose to significantly higher levels ($p<0,001$) than those of the caesarian section controls. There was no significant difference in the cord levels of bicyclo-PGEM in those fetuses that continued to exhibit FBM and those who did not.

Random blood glucose estimations (table 36) showed no differences of significance between the three groups or in the treatment groups at time of rescanning.

DISCUSSION

These results at term illustrate that the rapid rise in bicyclo-PGEM seen in the mid-trimester in chapter 5 occurs in the term pregnancy and to the same degree. This confirms the earlier work done by Gordon-Wright and Elder (1979) and MacKenzie et al (1980a) using the PGEM assay. It also confirms that large quantities of PGEM are found in the fetus (MacKenzie et al 1980a). Three fetuses were delivered within 1 hour of scanning and all had cord bicyclo-PGEM levels exceeding 600pg/ml.

From the FBM results in this chapter it is evident that the

TABLE 37

FBM RELATED TO CERVICAL DILATATION AND SCAN/DELIVERY INTERVAL

	CERVICAL DILATATION	SCAN/DELIVERY INT.
FBM Continued	2,8 ± 1,2 cm	5 ± 3,9 hrs.
FBM Ceased	5,75 ± 1,5 cm	3,1 ± 4,4 hrs.

administration of exogenous PGE2 does not inhibit FBM as 9 fetuses continued to have FBM. In the 6 fetuses that FBM ceased, 5 were in women in established labour. Table 37 indicates that these fetuses were in women who had cervices that were significantly more dilated ($p<0.01$) and who had significantly shorter scan/delivery intervals ($p<0,01$) than those where FBM continued, indicating that these patients were in active labour. As documented in the introduction and Part I of this thesis FBM diminishes to an insignificant incidence during active labour. Apnoea may thus be a product of the labour rather than the result of administration of the PGE2. In addition, a 30 minute recording for FBM is insufficient to conclude that FBM has ceased as normal apnoea at term may exceed 120 minutes (Patrick et al 1979). Thus it may be concluded that exogenously administered PGE2 does not suppress FBM.

Levels of PGE found in the neonate following therapeutic administration for ductus dependent congenital heart disease range from 63 pg/ml to 195 pg/ml (Silove 1982). The levels of bicyclo-PGEM in the cord blood of neonates born after maternal PGE2 administration vastely exceed this range. The levels in umbilical blood at fetoscopy in the mid-trimester are comparable with the therapeutic levels in the neonate. As described in the introduction, these levels are associated with a significant incidence of apnoea in the neonate in spite of the respiratory drive that is present post delivery.

The difficulty in establishing a direct relationship between PGE and FBM is created by two issues viz. our inability to assay the pharmacologically active prostaglandin in the blood, and our inability to collect samples of fetal blood at the time the

ultrasound examination is performed. The argument for considering that active PGE2 may reach the fetus has been documented in the previous chapter. From the above data it is inconclusive as to whether active prostaglandin crosses the placenta. Consequently, although the circumstantial evidence strongly suggests that PGE2 is not the mediator for suppression of FBM with the onset of labour, this too is inconclusive.

CHAPTER 8

FINAL DISCUSSION

This thesis has dealt with the use of real - time ultrasound in the assessment and management of preterm labour, with particular reference to the fetal biophysical parameters of fetal breathing movement and gross fetal body movement. It has also attempted to elucidate the relationship between PGE and the cessation of FBM with labour. An attempt has been made to define more clearly the problem that preterm labour presents to the Obstetrician and to clarify trends in preterm labour and neonatal outcome.

To summarise, my studies have revealed that, although the incidence of preterm labour has remained unaltered in Oxford between 1973 and 1981, neonatal outcome, both short and long term, following spontaneous "uncomplicated" preterm labour has greatly improved. Furthermore, morbidity in this group is minimal. With increasing evidence of the dangers of tocolytic therapy, the Oxford clinical findings suggest that the use of tocolysis should be reconsidered. Larger populations will have to be studied to be sure that the trends described are occuring elsewhere. Should this be so, the rationale for the continued use of tocolytics must be seriously questioned. This idea contrasts with recent suggestions from the United States (Stubblefield 1984), that more aggressive use of tocolysis should be employed.

Before assessment of treatment regimes can be made, diagnostic accuracy must improve. To help resolve this problem I have utilised the fetus' own behavioural patterns. The presence or absence of fetal breathing movement reliably predicts the outcome of preterm labour in patients with intact membranes and singleton pregnancies. This is not invariably so and my studies

have highlighted the influence that silent chorioamnionitis plays in the causation of preterm labour and in neonatal outcome. It is clear that if we are to consider tocolytic therapy in such patients advances must be made in the early detection of intrauterine infection.

The weight of evidence suggests that, with the majority of spontaneous "uncomplicated" preterm labours going on to delivery, occurring after 34 weeks of gestation, tocolysis is unwarranted. This is further supported by the potential risk of undiagnosed infection, as fetal biophysical parameters do not help detect infection. Evidence I have presented in a small number of patients indicates that in patients going on to deliver, as predicted by fetal apnoea, tocolysis made no difference to labour outcome. Thus, it would appear that although tocolysis may delay delivery for a few days, birth of the fetus almost inevitably occurs within a week. It is important to establish that this delay is not detrimental to the fetus by retaining it in a hostile environment. In this limited series no adverse effects could be demonstrated.

Curiously, the phenomenon of fetal apnoea with the onset of labour has not been found in preterm labour complicated by spontaneous rupture of the membranes or multiple pregnancy. The reason for this is unknown. It almost certainly relates to the mechanism of onset of the labour leading to the speculation that labours complicated by these two factors may have different modes of onset from singletons with intact membranes. Until we have clarified events leading to spontaneous term labour it is unlikely that this will be confirmed.

Although FBM has not been found to be of any prognostic

value in the presence of ruptured membranes, the subgroup of patients with ruptured membranes but normal liquor volume on initial scan, is interesting. In this group, FBM regained its prognostic significance when delivery occurred after 48 hours. Monitoring liquor volume was highly sensitive, for a notable reduction in volume reliably predicted the onset of contractions leading to delivery. These findings are of practical relevance in centres using corticosteroid administration to activate pulmonary maturation, for the time available for its administration to be effective may be indicated. It does not have any application with respect to tocolytic therapy, which would not be indicated in this clinical situation.

In labours complicated by antepartum haemorrhage FBM status was significantly related to labour outcome. Since this pathology precludes any form of intervention, the finding is only of academic interest.

The observation of fetal movements during preterm labour has no prognostic value with respect to labour outcome. It does, however, provide a sensitive index of fetal well-being. Lack of any significant fetal movement should alert the clinician to the fact that the fetus may be at risk. This is a simple observation that may be made on admission and could be determined from the fetal cardiotocograph by recording the accelerations on the trace. Real-time ultrasound provides a "window" through which FM can readilly be recorded.

Measurement of the cervix using real-time ultrasound has not proved to be of any prognostic value. This confirms previous clinical studies and clearly, until the cervix reaches the point where the diagnosis is self-evident, ie. 4cm or more, measurement

is of little value.

The second part of the thesis has considered the relationship between prostaglandin E2 and fetal breathing. My studies have elucidated the absorption profile of this substance when it is administered vaginally. This shows that PGE2 is rapidly absorbed into the maternal circulation during both the second and third trimesters, reaching a plateau by 60 minutes and maintaining this level for the following 5 hours. This has enabled the fetus to be studied during the time of maximal maternal circulating levels.

The information may also be of relevance for cervical ripening and labour induction. Uterine hypertonus is considered a major reason for not using prostaglandins. The level of myometrial activity (measured in Montevideo units) is directly proportional to the circulating level of bicyclo-PGEM (Castle et al 1983). This information and methodology may enable us to produce a more appropriate vehicle for the measured release of PGE2.

No direct relationship between PGE2 and fetal breathing could be conclusively established. The circumstantial evidence strongly suggests that PGE2 is not the mediator whereby fetal apnoea occurs with the onset of labour. However, until a direct assay for the active prostaglandin becomes available and until we can sample the fetus at the time of scan this will remain inconclusive.

It has been demonstrated that real-time ultrasound assessment is of real value in the management of preterm labour. This single investigation on a patient presenting in apparent

preterm labour enables the clinician to gain valueable information. The "traditional" measurements of fetal size and placental site estimation may be made and reassurance of fetal and placental normality gained. Accurate estimation of fetal weight can be made which is essential in the management of preterm labour at the bo rderline of fetal viability. The data presented in this thesis indicates that the assessment of fetal biophysical parameters is of value both for assessment of fetal well-being and the prediction of labour outcome. The cervix can be measured in the majority of cases with a high degree of accuracy obviating the need for vaginal examination.

It is to be recommended that real-time ultrasound plays an integral role in the management of the patient in preterm labour and that resident Obstetricians be trained in its use in the clinical situation.

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